

THE QUARTERLY JOURNAL OF MEDICINE

EDITED BY

**W. RUSSELL BRAIN
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A. M. COOKE**

**D. M. DUNLOP
H. L. MARRIOTT
ROBERT PLATT**

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NEPHRECTOMY AND OTHER TREATMENT FOR HYPERTENSION IN PYELONEPHRITIS¹

By G. W. PICKERING AND R. H. HEPTINSTALL

(From the Departments of Medicine and Pathology, St. Mary's
Hospital Medical School)

With Plates 1 and 2

EXCISION of one diseased kidney, the other being normal, has come to occupy a unique position in contemporary thought regarding the treatment and pathogenesis of hypertension. It offers one of the few prospects of complete cure—the others being excision of phaeochromocytoma, excision of cortical adrenal tumour, and repair of coarctation of the aorta—in a condition for which otherwise only treatments of slight and inconstant value exist, and it alone provides seemingly unequivocal evidence of the renal origin of certain forms of hypertension. For, while it is usual to group certain forms of hypertension, such as that occurring in acute and chronic glomerulonephritis, acute tubular necrosis, and polycystic kidney, as renal in origin, there is no direct evidence that this assumption is correct. Interest in this operation stems from two sources: first, the demonstration by Goldblatt and his colleagues (Goldblatt, Lynch, Hanzal, and Summerville, 1934; Goldblatt, 1938) that hypertension, resembling both benign and malignant hypertension in man, could be produced by constricting both renal arteries in the dog, and that a mild persistent hypertension could sometimes be produced by constricting only one renal artery; second, the observation of Butler (1937) that excision of a single diseased kidney in man abolished pre-existing hypertension. A spate of case reports has followed, but many of these have been single, and in all the follow-up period has been short. The present paper records the results of nephrectomy for hypertension in 11 patients seen by one of us (G. W. P.) in the last 11 years, together with a consideration of pyelonephritis, the chief renal lesion found, and its treatment.

The Results of Nephrectomy in 11 Cases

The results of nephrectomy are summarized in Table I and in the Appendix of case reports. The 11 cases may be conveniently grouped according to the lesion found in the kidney or kidneys.

Hypertension with unilateral renal tuberculosis. In this 50-year-old man (Case 1) hypertension was very slightly, if at all, affected by excising the diseased kidney, which showed extensive tuberculosis, with chronic non-specific pyelonephritis in the non-tuberculous tissue. A single exudate observed in the retina

¹ Received March 11, 1952.

TABLE I
Results of Nephrectomy

	Renal tuberculosis				Bilateral pyelonephritis				Unilateral pyelonephritis			
	Patient	2. V. C.	3. P. T.	4. J. M.	5. D. M.	6. G. C.	7. S. W.	8. G. N.	9. W. H.	10. G. L.	11. E. B.	
Age (years) and sex	50 M.	23 F.	13 F.	35 F.	26 M.	34 M.	16 M.	10 M.	46 M.	19 F.	33 M.	
Blood-pressure	230-250	166-196	240-255	210-250	180-186	215-240	220-260	170-190	190-230	210-230	220-240	
Fundus	135-185	104-117	160-180	145-160	110-115	140-145	150-175	130-140	120-140	125-150	148-170	
Exudate	Normal	Papilloedema	Normal	Normal	Papilloedema	Papilloedema	Papilloedema	Exudate	Normal	Papilloedema		
Renal function	Normal	Impaired	Impaired	Impaired	Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Duration	..	13 years	11 years	12 years	4 years	12 years	5 years	
Post-operative:												
Blood-pressure	200-244	166-192	210-230	200-260	150	132-160	210-230	160-180	190-210	140-170	160-170	
Fundus	125-150	100-120	160-170	140-170	90	98-110	135-170	115-125	110-140	90-110	110-120	
Renal function	Improved	Normal	No change	Papilloedema	Normal	Papilloedema	Papilloedema	No change	..	Normal	Normal	
Albuminuria	+	+	..	0	+	0	..	0	0	
Alive or dead	Dead	Alive	Alive	Dead	Dead	Alive	Dead	Alive	Alive	Alive	Alive	
Duration	25 months	9 years	5 years	9 months	10 days	10 years	7 months	5 years	3 months	10 years	5½ years	
Additional treatment	No	No	½ adrenalectomy	Sympathectomy	No	No	No	½ adrenalectomy	No	No	R. adrenalectomy, R. splenectomy neurectomy	

NOTE. The post-operative arterial pressures in Cases 3, 4, and 8 refer to the period after nephrectomy and before the subsequent additional operative treatment.

before operation regressed, but this has been observed to occur without treatment. Van Goidsenhoven and Vandenbrouck (1946) found hypertension in six of 92 cases of renal tuberculosis, and recorded two cases in which nephrectomy reduced hypertension, though in one a fistula remained, and in the other the tension fell slowly.

Bilateral pyelonephritis. In the first of these four patients (Case 2) the condition was suspected to be unilateral in spite of impaired renal function, and in spite of suggestive evidence of abnormality in the pyelograms of the other kidney and the presence of albumin in the specimen obtained from it by ureteric catheter. Nephrectomy did not affect hypertension, nor did it affect the progressive impairment of renal function, which led to urea retention nine years after operation. In Case 3 bilateral pyelonephritis was diagnosed, but as this girl of 13 years had gross hypertension, the diastolic pressure being 180 mm. Hg, and advanced hypertensive neuro-retinopathy (albuminuric retinitis), the more affected kidney was removed, but without definite benefit to the blood-pressure or retinae. Seven months later the whole of one and three-quarters of the other adrenal gland were removed at separate operations, supporting therapy with eucortone, deoxycorticosterone acetate, and salt being used as for an Addisonian crisis. No significant changes in serum-sodium or -chloride were observed, but she developed Addisonian pigmentation of the hands and the operation scars. Her blood-pressure fell, and her retinitis cleared. Five years after nephrectomy she is alive and working, but her retinae show gross arterial changes, and her blood-pressure is again very high. In another girl, aged 11 years, who had bilateral pyelonephritis (Case 2 of Pickering, Wright, and Heptinstall, 1952), and who showed gross hypertension (diastolic pressure 170 to 180), and advanced hypertensive neuro-retinopathy, no kidney was removed, but a similar adrenalectomy and an infradiaphragmatic sympathectomy were performed. These operations produced a striking fall of blood-pressure and resolution of the neuro-retinopathy, and she is alive and working, with only a moderate hypertension, five years after operation. In Case 4 the evidence for bilateral pyelonephritis was strong, and operation was not advised. She was a doctor's daughter and, persuaded by the favourable reports in medical journals, she went elsewhere and the more affected kidney was removed. Hypertension remained severe, bilateral hypertensive neuro-retinopathy developed, and in spite of a bilateral Smithwick sympathectomy, hypertension persisted unchanged and she died in uraemia one year after nephrectomy. In Case 5 the right kidney was removed after previous ligation of an aberrant artery and the removal of stones; death occurred on the 10th day from a pulmonary embolus.

Unilateral pyelonephritis. In six patients the excised kidney showed pyelonephritis, while no clinical evidence was obtained of this disease in the other kidney. Nephrectomy produced a gross and persistent fall of blood-pressure in three, but no fall, or a doubtful fall, in the remainder. In Case 6, as in Case 5 (both doctors), an aberrant renal artery had been divided, and in each case subsequent examination for life insurance showed a normal tension a few

months and three years after that operation. Ligation of a branch of the renal artery is thus not necessarily followed by hypertension. In both these patients hypertension began later, and may perhaps be attributed to the onset of pyelonephritis, though this suggestion is unsupported by the history. In Case 6 the hypertension can be ascribed to a renal cause, since nephrectomy reduced it conspicuously during the whole period of nine and a half years in which his progress has been followed. In Case 7, a boy of 15 years, the retinal changes of the malignant phase of hypertension had developed before nephrectomy. Subsequently the arterial pressure was unaltered, the neuro-retinopathy progressed, renal function declined, and he died of acute pulmonary oedema seven months after nephrectomy. *Post mortem* the remaining kidney showed gross lesions of malignant hypertension. A few areas of dense cellular infiltration resembling those of pyelonephritis were found, but the changes were very slight, and it seems very doubtful whether a pyelonephritis of this kidney was the cause of failure to respond to nephrectomy. In Case 8, a boy of 10 years, who had failing vision due to hypertensive neuro-retinopathy, nephrectomy produced a slight fall in blood-pressure but no retinal improvement. Four months later he had seven-eights of his adrenal tissue removed, as in Case 3; a further slight fall of blood-pressure and gradual resolution of his neuro-retinopathy resulted. He is alive and symptomatically well, but has moderate hypertension five years after operation. In case 9 nephrectomy produced little change in arterial pressure, but he was only seen once three months after operation. In Case 10 nephrectomy produced a moderate fall of arterial pressure, which rose again during a pregnancy five years later, to fall again after pregnancy was terminated. Ten years later the pressure remained about, or a little above, the upper normal limit, but she developed a subarachnoid haemorrhage with aphasia and hemiplegia. Case 11 had malignant hypertension, with a grossly raised blood-pressure and hypertensive neuro-retinopathy. His affected kidney and the adrenal gland, and the splanchnic nerves and upper lumbar ganglia on the same side, were removed. After operation his blood-pressure fell and his neuro-retinopathy cleared. He has remained well and at work, though with a persistent moderate elevation of his arterial pressure, during the subsequent five years.

Of these six cases, the evidence as to the state of the other kidney is complete only in Case 7, in which pyelonephritis was absent or slight. In the remainder pyelonephritis is presumed to have been absent from the other kidney, because no abnormalities were seen in the pre-operative pyelogram or in the urine after operation.

Discussion

The renal lesion. With the exception of the case of renal tuberculosis, the excised kidneys all showed similar changes to the naked eye and microscopically. They were reduced in size and coarsely scarred; the pelvis was dilated and expanded into the calyces, which were blunted and deformed; the kidney substance was reduced in amount. In the extreme case the renal substance was

reduced to a narrow rim of irregular thickness bounding the sac-like dilatation of pelvis and calyces (Plate 1, Fig. 1). In the two kidneys in which aberrant arteries had been tied the corresponding pole was atrophic. Microscopically the characteristic feature was the patchy distribution of lymphocytic infiltration in both cortex and medulla, with interstitial fibrosis and destruction of renal tissue (Plate 1, Fig. 2). In the larger kidneys these affected areas were separated by apparently normal renal tissue; in the smallest kidneys normal renal tissue was almost completely absent. In the affected areas the arteries and arterioles were greatly thickened, the thickening affecting the media and especially the intima, which showed productive endarteritis (Plate 1, Fig. 3). Arteriolar necroses were found in Cases 1, 3, 7, 9, and 11, in areas with and without chronic inflammatory changes (Plate 2, Figs 4, 5). These five cases were thus, pathologically, cases of malignant hypertension; clinically Cases 3, 7, and 11 showed hypertensive neuro-retinopathy; Cases 1 and 9 had only a few retinal exudates. The glomeruli in the affected areas showed various stages of degenerative lesions, with periglomerular fibrosis as an early and conspicuous change, and hyalinization or complete disappearance as a later development. The latter was a very striking feature. The tubules were dilated, were lined by atrophic epithelium, and contained eosinophile amorphous casts, thus closely resembling thyroid tissue in the haematoxylin-and-eosin stained sections (Plate 2, Fig. 6). When active inflammation was present there were polymorphs in the tubules. Lymphocytes, and even lymphoid follicles, were present in large numbers under the pelvic epithelium, and the pelvis showed increased fibrosis.

Renal lesions of this type were described by Lölein in 1917 as a special form of secondarily contracted kidney, the pyelonephritic type. His three cases were in young women who died of uraemia, hypertension being present in two. Subsequent papers by Staemmler and Dopheide (1930) and Pfeiffer (1932) gave accurate pictures of the morbid anatomy of the condition. Gibson (1928) in his Bradshaw Lecture gave a good description of atrophic pyelonephritis and its evolution from the acute form. But its recognition in the English-speaking world is largely due to the work of Longcope and Winkenwerder (1933), who described accurately the clinical and pathological features of the condition and emphasized its frequency. Weiss and Parker (1939) also emphasized its frequency, finding the condition in 15 to 20 per cent. of patients with malignant hypertension who came to autopsy in the Boston City Hospital. The above papers deal particularly with bilateral pyelonephritis, but Haslinger (1928) and Jacoby (1930) paid particular attention to the unilateral form. In spite of this work, many morbid anatomists and clinicians in this country are unfamiliar with the condition.

Chronic atrophic pyelonephritis may, as Gibson emphasized, occur secondarily in a kidney already rendered abnormal by a lesion such as a calculus, or primarily in a kidney apparently previously healthy. The disease, by producing focal inflammation and destruction of renal tissue, leads to scarring, lobulation, and shrinkage of the kidney. Thus many of the appearances found in the

kidneys of our patients may be attributed to the pyelonephritic process. An alternative explanation was put forward by Ask-Upmark (1929) who described eight cases, six of them in children or young adults, in which malignant hypertension was associated with peculiar changes in one or both kidneys. These changes were threefold: (1) unilateral renal hypoplasia; (2) deformity of one or both kidneys; (3) the presence in one or both kidneys of peculiar recesses of the renal pelvis, ending blindly near the surface of the kidney. He thought that these changes were developmental in origin, and due to a faulty relationship in growth between the kidney and ureteric *Anlagen*. The gross and histological appearances of these kidneys were similar to those here described, and it seems probable from the description of focal round-cell infiltration that most or all were affected by pyelonephritis. A developmental fault and pyelonephritis are by no means antithetic. Especially in unilateral cases it seems likely that pyelonephritis may be grafted on to a renal abnormality. The nature of this abnormality is by no means certain, but the tendency to pelvic dilatation, and the presence in two patients of intermittent hydronephrosis, necessitating ligature of an aberrant renal artery, suggest that interference with renal pelvic outflow may have been an important component. But although we may see these two processes combined to produce the unilateral renal disease here considered, it seems probable that the factor related to hypertension is not a developmental renal fault, but pyelonephritis. While simple hydronephrosis is not accompanied by hypertension, hypertension in hydronephrosis is in our experience always associated with pyelonephritis, although we have made no large-scale investigation to decide this point. In two of our patients (Cases 5 and 6) the evidence is convincing that hypertension did not develop until early adult life.

Clinical features of pyelonephritis. The clinical recognition of pyelonephritis may be very difficult, especially when it is apparently unilateral; in four patients of the present series (Cases 7, 8, 10, and 11) the condition was entirely symptomless, and was detected only when a non-excreting kidney was found on intravenous pyelography. In three others there were no symptoms when the condition was discovered and nephrectomy performed, though symptoms had been present many years before. The condition may complicate ureteric or pelvic obstruction by a stone or other lesion. Calculus had occurred in one of our patients (Case 5), and an aberrant renal artery in two (Cases 5 and 6); the cause of the small hydronephrosis was not apparent in the remainder. The usual symptoms are fever, frequency of micturition, pain or scalding on micturition, and attacks of pain in the back, or renal colic. Physical signs are inconstant, except albuminuria, varying from a trace to a moderate amount, and an excess of white cells in the urine, best revealed by an Addis count, with or without an excess of casts. In bilateral chronic atrophic pyelonephritis renal function is usually, often grossly, impaired, but in unilateral cases it remains normal until malignant hypertension supervenes. Pyelography usually reveals abnormalities in the pelvis and calyces, and is a most important investigation, to which further reference will be made. As Longcope (1937) pointed out, the

clinical condition may remain unchanged for years, it may periodically relapse and remit, or it may progress to renal failure without hypertension. In other patients hypertension is the dominant symptom, and may take the malignant course.

The relationship of hypertension to pyelonephritis. Longcope (1937), Weiss and Parker (1939), and others have shown that not all patients who have pyelonephritis develop hypertension, and it is uncertain why this is so. Longcope made a detailed comparison of post-mortem findings in chronic atrophic pyelonephritis with and without hypertension. 'In four fatal cases in which the blood pressure remained within normal limits or was only slightly elevated . . . the arterioles of the kidney, pancreas, adrenals and intestines appeared normal.' 'In three cases in which hypertension was marked and was one of the outstanding features of the clinical course, a few arterioles were found in the kidney, pancreas, adrenals and intestines which showed moderate hyaline sclerosis, but the lesions were almost minimal in extent.' He concluded: 'The explanation for the hypertension occurring particularly during the later stages of the contracted kidney of pyelonephritis is not clear.'

The kidneys in all our patients, even in the youngest, showed proliferative changes in the arteries and arterioles in the affected areas. In most cases these changes were gross, but in Cases 5, 6, and 8 the vascular change was slight. In the least affected kidneys the abnormal vessels in and around the inflammatory foci were in striking contrast to the relatively normal vessels in the normal renal parenchyma. Thus the proliferative vascular change would appear to be a product of local inflammation, as in chronic inflammation elsewhere. That this renal vascular change may be related to hypertension was suggested by Weiss and Parker (1939), who stated on the basis of 100 necropsies that: (1) a mild degree of hyperplastic arteriolosclerosis in both kidneys is usually associated with normal blood-pressure; (2) a severe degree of hyperplastic arteriolosclerosis in unilateral pyelonephritis may or may not be associated with hypertension; (3) a severe degree of hyperplastic arteriolosclerosis in both kidneys is almost always associated with severe hypertension. These arterial changes are to be carefully distinguished from the arteriolonecrosis of malignant hypertension, which is a consequence of severe hypertension (Wilson and Pickering, 1937-8; Wilson and Byrom, 1939, 1941; Byrom and Dodson, 1948), and was found not only in the kidneys but in the excised adrenal glands of our cases of malignant hypertension. In the kidneys these necrotizing lesions occurred not only in the pyelonephritic areas, but throughout the entire kidney. Longcope (1937) presumably refers to these lesions when he speaks of hyaline sclerosis.

Goldring and Chasis (1944) have summarized the evidence for a very different view, namely, that pyelonephritis does not produce hypertension. Briefly, their evidence, obtained from the figures given by several groups of authors, is (1) that the incidence of hypertension is not greater in patients with pyelonephritis than in a control series, and (2) that in patients with apparently unilateral renal disease nephrectomy does not normally relieve hypertension.

They reviewed 76 published case reports describing the effects of unilateral nephrectomy on blood-pressure. In 37 of these subjects the operation was considered successful, but after critical review Goldring and Chasis rejected 30 of these cases, because blood-pressure did not fall into the normal range (eight cases) or returned to hypertensive levels within six months (two cases), and because control observations (one case) or post-operative follow-up (19 cases) were inadequate. They considered that an incidence of only one in ten of relief of hypertension by nephrectomy is inadequate evidence to establish the relationship between unilateral renal disease and hypertension. This is probably not a correct estimate of the incidence of relief from hypertension by nephrectomy; cases in which the information is inadequate cannot necessarily be regarded as failures, and published cases are probably not truly representative.

Nephrectomy for hypertension. Of our 11 cases in which nephrectomy was undertaken for hypertension, the operation was strikingly successful in three (Cases 6, 10, and 11), in which the average fall of blood-pressure was 85/40, 65/35, and 70/45, maintained for nine and a half, ten, and five and a half years respectively. Nevertheless, even in these three cases the arterial pressure remained higher than the accepted normal, and in one patient (Case 10) responded to pregnancy with a further increase. One patient (Case 5) died of the operation. The remaining seven experienced little, if any, benefit, and in one (Case 4) the expectation of life may have been reduced. These results are not quite in harmony with published cases. Thus Langley and Platt in 1947 analysed 93 published cases, of which one, a success, had been previously published by Platt; they added 10 further cases of their own, nine failures and one partial success. Of the 93 previously published cases 47 were classed as successes, 28 as failures, five as partial successes, and 13 as doubtful. Since many of these published cases are single reports, and since the prevalent tendency among doctors is probably to report success rather than failure, it is probable that these cases exaggerate the frequency of relief of hypertension. The results of published series containing five cases or more are summarized in Table II. Of these series, that of Barker and Walters (1940) sets out only to describe successes; how many of their cases of operation were failures is not known. The other reports probably represent continuous series, but some of them contain little detail. Omitting the series of Barker and Walters, there were 21 successes or partial successes against 32 failures, a proportion similar to our own three successes and seven failures, if we omit the post-operative death. Thus in representative series the operation seems to have failed more often than it has succeeded in lowering arterial pressure. Many of these failures are due to bilateral disease. In the series of Langley and Platt two failures, and in that of Schroeder and Fish four failures, were in cases of bilateral disease. The cases of van Goidsenhoven and Vandebrouck were all said to be unilateral. Bilateral disease accounted for three of the seven failures in the present series. In our bilateral cases excision of the more affected kidney did not significantly reduce blood-pressure, and in Case 4 it may have accelerated renal failure. In bilateral disease nephrectomy is not indicated. Of our remaining seven cases

of presumed unilateral disease, nephrectomy failed to lower blood-pressure materially in four. In Case 1 the kidney was the seat of tuberculous disease, a process not generally believed to produce hypertension; the patient had a previous history of calculus, and may have had an abnormal remaining kidney, or he may have had essential hypertension. Cases 1, 7, and 9 showed arteriolar necroses in the excised kidney, and clinically Case 8 had entered the malignant phase; on the hypothesis of Wilson and Byrom (1941) the arteriolar lesions in the other kidney may have maintained the hypertension, though this is unlikely

TABLE II
Series containing Five or More Cases of Nephrectomy for Hypertension

Authors	Number of cases	Successes	Partial successes	Failures
Barker and Walters (1940)	5	5
Palmer, Chute, Crone, and Castleman (1940)	9	1	..	8
Nesbit and Ratliff (1941)	10	6	..	4
Schroeder and Fish (1940)	7	2	..	5
Van Goidsenhoven and Vandenbergrouck (1946)	16	8	2	6
Langley and Platt (1947)	11	1	1	9
Pickering and Heptinstall (1952)	10	3	..	7

in Case 8, in whom arteriolar necroses were not found in the excised kidney or adrenal glands, nor in a biopsy specimen from the unexcised kidney. In this respect Case 8 may be contrasted with Case 11, in whom arteriolar necroses in adrenal and kidney were abundant, and yet nephrectomy conspicuously reduced hypertension. In Case 8 there was no evidence of a lesion of the other kidney, though the biopsy of the unexcised kidney necessarily gave information limited to the fragment removed. The probability of undetected bilateral disease is strengthened by considering Ask-Upmark's series of necropsies, for of his seven patients with grossly unequal kidneys four had bilateral disease.

While we feel, therefore, that the most probable cause of failure of nephrectomy in pyelonephritis is affection of the other kidney, two other possibilities must be considered. It is possible that hypertension of long enough duration becomes irreversible. A suggestive analogy may be seen in the rabbit with hypertension produced by constricting one renal artery, the other kidney having been previously removed; excising the ischaemic kidney after one week abolishes hypertension, while excising it after two months leaves hypertension unaltered (Pickering, 1944-5). The hypertension here is, however, reversible, for if the clamp is removed after two months and the kidney left *in situ*, the hypertension is slowly abolished (Blacket and Sellers, 1951). Schroeder and Fish (1940) suggested that nephrectomy was unlikely to relieve hypertension that had been present for more than two years. The analysis by Langley and Platt (1947) showed that this was not true, as is exemplified by our Case 6, in whom hypertension known to exist for five years was relieved by nephrectomy. A second possibility is that hypertension in such cases is not due to the renal

lesion at all. This may have been so in Cases 1 and 9, both of whom had entered the age-group in which hypertension is common, but it is very improbable in Cases 7 and 8, both young boys with malignant hypertension. Moreover, the striking effect in Cases 6 and 10, in whom a sustained fall of pressure followed excision of a kidney with similar histological changes, makes it probable that in some way the kidney was responsible for hypertension. The effect of nephrectomy was even more striking in Case 11; the associated unilateral adrenalectomy and sympathectomy have not produced significant changes of arterial pressure in other cases, and probably played little part in the effect in this case. While we agree with Goldring and Chasis (1944) that published results often contain too little information to establish a relationship between nephrectomy and relief of hypertension, we consider that the pre-operative and post-operative observations were so long in our series that the result is established in these three cases. In fact these and similar cases provide convincing, and the only, evidence that a renal lesion can cause hypertension in man. Presumably hypertension in these cases is the result of some humoral influence of the kidney, but this has not yet been accurately defined and measured, even in the experimental animal whose renal arteries have been constricted. The fact that the arterial pressure remained appreciably above normal after nephrectomy, even in those cases in which operation produced its most striking effect, is entirely in conformity with our experience of excising a phaeochromocytoma in sustained hypertension (Barnett, Blacket, Depoorter, Sanderson, and Wilson, 1950).

We conclude that, in some cases at least, the cause of the hypertension can be ascribed with confidence to a renal lesion, but we are not in a position to state exactly what this lesion is. The relationship of pyelonephritis and of its associated renal vascular change to hypertension has already been discussed, and it will be realized that the conflicting evidence does not enable any final conclusion to be drawn as to which, if either, of these changes is responsible for the onset of hypertension.

Other measures for the relief of hypertension. Since nephrectomy is unlikely to relieve hypertension in bilateral cases, and is successful in only about half of apparently unilateral cases of pyelonephritis, other measures must be considered, especially when the accession of hypertensive neuro-retinopathy indicates the imminence of death if the arterial pressure is not reduced. Sympathectomy is one such measure that may prove successful, but the present series contains too few data to justify comment. In three children in the malignant phase (Cases 3 and 8, and Case 2 of Pickering, Wright, and Heptinstall, 1952) removal of the whole of one and three-quarters of the other adrenal gland was tried on the analogy of Goldblatt's (1937) experiments, in which hypertension following constriction of the renal artery was abolished by adrenalectomy. In the patient reported elsewhere a subdiaphragmatic sympathectomy of the Adson type was also carried out. In all these cases serum-electrolytes were controlled by salt, deoxycorticosterone acetate, and eucortone, begun before and continued after the operation for two to four

weeks. Addisonian pigmentation developed in only one case. All these three patients responded well, and are still alive, though no supporting therapy has been given for about five years. A similar adrenalectomy was employed without success in three adults who had malignant hypertension not due to pyelonephritis. Two died early in the post-operative period, one in coma, with a high level of sodium in the serum and cerebrospinal fluid, and one from haemorrhage. In the other patient hypertension was little affected. Whether these different results are due to age, or to a specific effect of adrenalectomy on the presumably renal hypertension of pyelonephritis, or to chance, cannot be decided from our limited data. With the advent of the pentamethonium and hexamethonium compounds a new possibility of controlling hypertension in pyelonephritis is opened.

Malignant hypertension. In their classical work on Bright's disease in 1914 Volhard and Fahr pointed out that essential hypertension might follow one of two courses, benign and malignant. In benign hypertension the hypertension was moderate or mild, the retina usually normal, and the expectation of life good, and death was due to cardiac failure, apoplexy, or intercurrent disease. In malignant hypertension the hypertension was more severe, the retina showed hypertensive neuro-retinopathy, and death usually occurred from uraemia within a year of the retinal lesion. The nature of the malignant phase of hypertension has been discussed before (Pickering, 1942) and will be dealt with more fully elsewhere. Here it will suffice to remark that clinical deterioration is due to arteriolar necroses, which expand the vessel wall at the expense of its lumen. These necroses are most frequent and severe in the kidney, and they lead to progressive functional impairment and finally renal failure. Experimental evidence suggests that they are due to the gross rise of intra-arterial pressure (Wilson and Pickering, 1937-8; Wilson and Byrom, 1939, 1941; Byrom and Dodson, 1948), and it might be anticipated that these lesions would be arrested if the arterial pressure fell below the critical level. This suggestion is borne out by the results in the present series of patients, for reduction of arterial pressure below the critical level led to survival for at least five years in Cases 3, 8, and 11, in whom hypertensive neuro-retinopathy indicated the onset of the malignant phase. Conversely in Case 7, in whom no fall of pressure occurred, and in Case 4, in whom hypertension increased, the disease progressed to its inexorable end. While life insurance statistics show that expectation of life and arterial pressure are inversely related, it is the onset of the malignant phase that makes it imperative to reduce the degree of hypertension if life is to be saved.

Practical suggestions. From the above experiences the following suggestions are made:

1. Since unilateral pyelonephritis can occur without more than a trace of albumin and with normal renal function, intravenous pyelography is indicated in all patients who have malignant hypertension not in the terminal stage, and in all patients under 40 years of age with severe hypertension not due to coarctation of the aorta, Cushing's syndrome, or nephritis.

2. Apparent failure of one kidney to excrete the dye may mean that that kidney is grossly diseased; but it can occur in subjects with normal kidneys, and before a diagnosis of unilateral disease is accepted intravenous pyelography should be repeated. In three patients referred to one of us (G. W. P.) repetition of intravenous pyelography showed the apparently non-excreting kidney to be normal.

3. If unilateral disease is suspected from intravenous pyelography and normal renal function, the ureters should be catheterized, a urea-concentration or similar test done on the two sides, and the urine cultured and examined for cells and albumin. Abnormalities of the urine obtained from the supposedly normal kidney make bilateral disease probable, but renal function tests must be interpreted with caution owing to the sources of error involved.

4. If as a result of these investigations it is concluded that the disease is unilateral, excision of the affected kidney is justified, and may be expected to relieve hypertension in about half the cases.

5. If the condition is apparently bilateral, removal of the more affected kidney is unlikely to do good, and may do harm. Nephrectomy is generally contra-indicated if total renal function is impaired.

6. If hypertensive neuro-retinopathy is present, relief of hypertension is imperative. In unilateral cases in which nephrectomy has failed, or in bilateral cases, the following measures may be employed to reduce the arterial pressure below the critical levels: (1) parenteral administration of hexamethonium compounds, as recommended by Smirk and Alstad (1951). This measure was not tried in the present series; (2) subtotal adrenalectomy, with adequate pre- and post-operative care. This was successful in the present series; (3) sympathectomy, which was not adequately investigated in the present series.

Our thanks are due first to our patients, who have co-operated so readily in the follow-up studies, and secondly to our colleagues for referring patients to us. We wish particularly to thank Professor Harold Scarborough, who co-operated in the study of four of these patients, Professor W. D. Newcomb for helpful advice regarding the pathology, and Mr. A. Dickson Wright for his unrivalled surgical skill and his unfailing helpfulness.

Case Reports

Case 1. M. S., a man born in 1889, was admitted to Harefield Hospital in December 1939. He had had bilateral epididymo-orchidectomy 19 years before for tuberculosis. In August 1939 he had haematuria, followed by left renal colic and suppression of urine. The left kidney was decapsulated; a stone was passed later. High blood-pressure was first observed in August 1939. Examination showed a eunuchoid appearance. The blood-pressure was 245/135. The fundi showed no papilloedema, bilateral small white glistening exudates, and an ill-defined exudate in the right eye. On intravenous pyelography the right kidney was functionless and appeared small; the left kidney was large and its function poor. The blood-urea was 38 mg. per 100 ml., and urea concentration 3.3 per cent. Urine culture was sterile, and no tubercle bacilli were seen. He was readmitted on July 25, 1940; the blood-urea was 34 mg. per 100 ml., and

the urine contained a few pus cells and albumin. The blood-pressure varied between 230/150 and 250/185. The right kidney was removed on September 30, 1940. After a post-operative fall to 75/60 the blood-pressure rose, and varied between 200/125 and 220/150. The fundi showed no change on November 3, 1940. He was last seen on May 11, 1942; he had been free from headaches since nephrectomy, the blood-pressure was 244/130, and the fundi showed no papilloedema. He died on October 28, 1942, the cause of death being given on the death certificate as uraemia.

Examination of kidney. *Macroscopic:* right kidney $9 \times 4 \times 4.5$ cm. Typical picture of renal phthisis. Pelvis not greatly enlarged, calyces spherical and dilated, the largest being 3.7 cm. in diameter. All are filled with caseous material. *Microscopic:* typical renal tuberculosis, but with changes of chronic non-specific pyelonephritis in non-tuberculous areas. Vascular changes are very conspicuous in the latter areas, and consist of fine collagenous proliferation of the intima in the smaller arteries and necrotizing lesions in the arterioles.

Case 2. V. C., a woman born in 1918, had a fainting attack in October 1941. She gave a history of frequency of micturition at the age of 10 years, when she was in bed for two weeks; she had no haematuria, and had no recurrence. Her father died of bronchopneumonia at 59 years of age; her mother was well, aged 53 years; three brothers and one sister were alive and well. On examination the arterial pressure varied from 166 to 196 systolic and from 104 to 117 diastolic. The heart was not enlarged. The fundi were normal. The urine showed albumin, red cells, and pus; culture yielded *Bact. coli* on four occasions. The blood-urea was 46 mg. per 100 ml., and urea clearance 36 per cent. and 57 per cent. of normal. An intravenous pyelogram showed a right kidney larger than normal, with abnormal distribution of calyces, and an extremely small left kidney. On catheterization urine from the right ureter contained 18 mg. albumin per 100 ml., 1.37 per cent. urea, and many red cells; culture was sterile. A retrograde pyelogram of the right kidney showed abnormal distribution of the calyces and a suggestion of pressure on the lower part of the renal pelvis. Catheterization of the left ureter showed faint excretion of indigo carmine; culture was sterile. A retrograde pyelogram showed a small left kidney with some hydronephrosis. The left kidney was removed on March 26, 1942. After a post-operative fall, the blood-pressure varied in the next month from 166 to 192 systolic and from 108 to 120 diastolic. In 1944 she became pregnant; the blood-pressure was 165/90. A bicornuate uterus, with pregnancy in one horn, was removed on August 30, 1944. The blood-pressure rose to 230/150 in December 1944, but there was no other change. In January 1951 she was admitted to hospital with bilateral pulmonary tuberculosis. The blood-pressure was 180/100. The urine contained pus, granular casts, and 0.9 gm. albumin per litre; culture yielded enterococci sensitive to chloramphenicol, and no tubercle bacilli. The blood-urea was 52 to 75 mg. per 100 ml., and urea concentration 1.9 per cent. An Addis count showed 218,000 red cells, 1,100,000 white cells, and 310,000 casts in 12 hours. An intravenous pyelogram showed a right kidney with minimal calyceal dilatation and moderate pyelectases. Streptomycin, chloramphenicol, and *p*-aminosalicylic acid produced no significant change in her condition.

Examination of kidney. *Macroscopic:* left kidney small and coarsely scarred; pelvis and calyces dilated and inflamed; parenchyma reduced in amount (Plate 1, Fig. 1). *Microscopic:* typical lesions of chronic pyelonephritis with superadded acute infection. In the scarred areas the arterioles and small arteries are thickened by intimal proliferation, and to a lesser extent by medial

hypertrophy, sometimes associated with fibrosis. The vessels in the non-pyelonephritic areas are relatively unaffected.

Case 3. P. T., a girl born in 1933, was first seen by Dr. Donald Paterson at Great Ormond Street Hospital in June 1946, on account of headache and listlessness for four years and vomiting for one month. When two and a half years old she had attended Tite Street Clinic because of attacks of listlessness. Her father, aged 38 years (blood-pressure 124/82), and mother, aged 39 years (blood-pressure 136/90), were both well. On examination her blood-pressure was 255/180. The fundi showed bilateral hypertensive neuro-retinopathy. The urea clearance was 48 per cent. and 56 per cent. of normal, and the blood-urea 82 mg. per 100 ml. The urine contained albumin 0·1 per cent., and culture yielded *Bact. coli*. An intravenous pyelogram showed some pelvic dilatation on both sides; the left kidney was smaller, excreted less well, and had a large double ureter. The left kidney was excised on July 3, 1946; it was small, adherent, and fibrotic. After a post-operative fall to 160/95, the blood-pressure rose to 210/170. There was no other change in her condition. On January 28, 1947, she was admitted to St. Mary's Hospital. The blood-pressure was 230/170. The fundi showed hypertensive neuro-retinopathy; the blood-urea was 32 mg. per 100 ml., and urea concentration 2·7 per cent. On February 13, 1947 three-quarters of the right adrenal was removed, and biopsy of the right kidney performed. The blood-pressure was not greatly altered. On April 24, 1947 the left adrenal was removed entire; the splanchnic nerves were untouched. Pre-operative and post-operative treatment was given with deoxycorticosterone and cortical extract. The blood-pressure fell to 170/104 on April 26, and remained between 150/110 and 210/170 until the patient was discharged on May 23, 1947. On September 25, 1947 conspicuous Addisonian pigmentation was present. Papilloedema had disappeared. The blood-pressure was 185/148. On August 22, 1951 the blood-pressure was 235/155. The urine contained albumin and a slight excess of white cells. Pigmentation was less. The fundi showed gross arterial changes, and no exudates.

Examination of kidney. *Macroscopic:* kidney $6 \times 2\cdot5 \times 1\cdot5$ cm., with coarsely nodular surface. There are two ureters, one draining the upper calyx, and the other draining the remainder of the kidney. The pelvic wall is thickened, and the calyces somewhat dilated. The cortex is reduced to 0·2 cm. in the scarred areas. *Microscopic:* typical lesions of chronic pyelonephritis. The pelvic inflammatory reaction is greater than usual, and lymphoid follicles are present. Vascular changes are pronounced, and necroses are found in arterioles and small arteries, both in scars and in non-scarred areas (Plate 2, Fig. 4). Fine intimal proliferation is present in the small arteries in the scarred areas, but is minimal in the non-affected areas. Elastic reduplication is seen in arteries of all sizes. *Microscopy of adrenals:* fibrinoid necroses in vessels in the substance of the gland and in the periadrenal fat.

Case 4. J. M., a married woman, born in 1911, was admitted to St. Mary's Hospital on September 10, 1946. Since 1937 she had had intermittent attacks of frequency and pyuria. In 1940 her blood-pressure was 130/80, and the blood-urea 40 mg. per 100 ml. In November 1941 a pregnancy was terminated on account of urinary infection. On April 26, 1946, parturition was induced three weeks before term; a living child was born. The blood-pressure had risen from 150/100 early in pregnancy to 160/120. The blood-urea was 34 mg. per 100 ml. The urine contained much albumin and pus; culture yielded *Bact. coli*. On examination in September 1946 the blood-pressure varied from 124/90 to 148/110. The blood-urea was 26 mg. per 100 ml., and urea concentration 2·4

per cent. The urine contained albumin and pus; culture yielded *Bact. coli* on two occasions. An intravenous pyelogram was technically unsatisfactory owing to gas; both kidneys and ureters were seen. The fundi were normal. The diagnosis was chronic *Bact. coli* urinary infection with bilateral pyelonephritis; nephrectomy was not advised. She was treated with sulphonamides. In June 1949 she complained of right-sided abdominal pain and haematuria, and was admitted to New End Hospital. The urine contained albumin and pus cells; culture yielded *Staph. albus*. The blood-urea was 34 mg. per 100 ml. Intravenous and retrograde pyelograms showed a functionless left kidney and a small hydronephrosis of the right kidney. The blood-pressure varied between 210 and 250 systolic and between 145 and 160 diastolic. On September 1, 1949 the left kidney was removed. The blood-pressure remained stationary about 200/140 and 220/166. On September 20, 1949 urea concentration was 1.1 per cent.; urea clearance was 27 per cent. of normal. On her discharge the fundi showed advanced bilateral hypertensive neuro-retinopathy. On October 11, 1949 her blood-pressure was 260/170. She complained of attacks of breathlessness at night. Right thoraco-lumbar sympathectomy was done November 17, 1949. The blood-pressure remained unchanged. She died in uraemia on June 15, 1950.

Surgically excised kidney. *Macroscopic:* small contracted kidney, $4 \times 2.3 \times 1.8$ cm. Subcapsular surface coarsely granular. There is dilatation of calyces and pelvis, and the parenchyma is reduced to 2 mm. in places. *Microscopic:* appearances of chronic pyelonephritis of extreme type. In the scarred areas there is hyalinization of arterioles, and fine collagenous proliferation in the intima and medial thickening of small arteries. There is some fibrosis in the media. Vascular lesions are not so pronounced in the relatively normal areas, although there is very little normal tissue left.

Kidney removed post mortem. *Macroscopic:* very small and granular; calyces and ureter dilated. *Microscopic:* chronic pyelonephritis of a very diffuse type, with evidence of recent acute infection. Vascular changes are similar to those seen in the surgically excised kidney.

Other post-mortem findings were insignificant except for hypertrophy of the left ventricle of the heart.

Case 5. D. M., a male doctor, born in 1914, had suffered from attacks of right renal colic and haematuria for four years. In January 1939 a right renal calculus and hydronephrosis were demonstrated radiologically. In February 1939 an aberrant right renal artery was tied and cut. A few months later he was examined for life insurance. The blood-pressure was normal. In July 1940 he had left renal colic. Bilateral renal calculi were demonstrated by X-rays. In August 1940 the stones were removed from the right renal pelvis. In September 1940 the patient noticed high tension of his pulse. His blood-pressure was 180/110. The urine contained a trace of albumin. In December 1940 he was admitted to Harefield Hospital. The blood-pressure was 186/115; the heart was not enlarged. The urine contained albumin and red and white cells; culture was sterile. Blood-urea was 25 mg. per 100 ml.; urea clearance was 53 per cent. of normal. X-rays showed bilateral renal stones and right hydronephrosis. On January 16, 1941, the right kidney was removed. The blood-pressure fell to 134/85, and rose to 150/90 on the eighth day. On the 10th day he died of pulmonary embolism. No post-mortem examination was made.

Examination of kidney. *Macroscopic:* kidney $10 \times 5 \times 4$ cm. Part is congested, and part pale. A fibro-fatty mass is adherent to a shrunken lower pole (the

part supplied by the tied aberrant vessel). *Microscopic*: lower pole presents appearance of an organized infarct. Remainder of kidney shows changes of hydronephrosis and patchy pyelonephritis. A minute calculus is adherent to part of pelvis. Vascular changes are insignificant, except some endarteritis of larger arteries.

Case 6. G. C., a male doctor, born in 1908, between 1924 and 1929 suffered from repeated attacks of right renal colic. In 1929 the urine showed pus cells, and on culture grew *Staph. albus*. At operation the right kidney showed a hydronephrosis about 5 cm. in diameter, with a stricture at the ureteropelvic junction caused by an aberrant renal artery. The aberrant vessels were divided and the stricture repaired. In 1932 his blood-pressure was stated to be normal at life-insurance examination; the urine contained no albumin. In March 1937 he was rejected for life insurance because of hypertension. His blood-pressure was then 170/110. In 1938 his blood-pressure was measured thrice, and was 158 to 170 systolic and 110 to 115 diastolic. In 1939 an intravenous pyelogram showed little excretion from the right kidney. The blood-urea was 39 mg. per 100 ml.; the urea clearance was 65 per cent. of normal. The urine contained no albumin or excess of cells. In 1941 he had occipital headaches on waking; the blood-pressure was 215/145, the blood-urea 33 mg. per 100 ml., and the urea clearance 85 per cent. of normal. The fundus showed no neuro-retinopathy. In February 1942 the blood-pressure was 226/145. In March 1942 he was admitted to King's College Hospital. The blood-pressure was 240/140. On March 16, 1942 the right kidney was removed. On March 17, 1942 the blood-pressure was 140/96. From 1942 to 1951 his blood-pressure was measured 18 times, and varied between extremes of 132 and 150 systolic and 98 and 110 diastolic. After operation he had complete relief from morning headache, and noticed an increased frequency of Raynaud's phenomenon on cold days. In 1951 he remains at work as a pathologist in excellent health. The urine and renal function remain normal.

Examination of kidney. *Macroscopic*: kidney 8×4×4 cm. Surface coarsely scarred, with thickened and partially adherent capsule. The pelvis and calyces are widened, with a few small haemorrhages. The parenchyma in general is reduced in width, but at the lower pole it is considerably reduced and fibrous. *Microscopic*: Appearances are those of hydronephrosis with patchy areas of chronic pyelonephritis. Intimal thickening of arteries is seen in the scarred areas.

Case 7. S. W., a toolmaker, born in 1927, had a haemoptysis in March 1942. His father was alive; his mother had died of tuberculosis; one sister and one brother were well. On examination in May 1942 the blood-pressure was 240/160, and the heart was slightly enlarged. The urine contained no pus or red cells, and was sterile on culture. The blood-urea was 37 mg. per 100 ml. Urea clearance was 74 per cent. of normal. An intravenous pyelogram showed a normal right kidney, the left kidney not excreting. A second intravenous pyelogram showed poor excretion in a very small and poorly developed left kidney. On catheterization the right ureter yielded 10 ml. of urine with 1.5 per cent. urea, and the left 1 ml. with 0.9 per cent. urea. On May 20 papilloedema and exudates were seen in both eyes. On May 27, when the blood-pressure had remained between 220 and 260 systolic and between 150 and 175 diastolic since his admission, the left kidney was removed. The blood-pressure fell to 190/150, and rose later to 210/170; measured at intervals, it remained above 210 systolic and 135 diastolic. The patient was discharged on July 2, 1942, and readmitted in January 1943 for cardiac asthma. On readmission the blood-pressure was

190/115, with pulsus alternans and gallop rhythm. The fundi showed gross hypertensive neuro-retinopathy. The blood-urea was 76 mg. per 100 ml. The urine contained albumin and a few pus cells. On January 27, 1943 he died in another attack of pulmonary oedema.

Surgically excised kidney. *Macroscopic:* size $4.5 \times 2 \times 1.5$ cm.; weight 12.0 gm. The surface of this grossly reduced kidney is coarsely granular. Pelvis and calyces appear dilated because of gross parenchymal reduction. There is great thickening of the pelvis. Vascular supply is through three small vessels, one to each pole and one to the centre. *Microscopic:* changes of chronic pyelonephritis. Medial and intimal thickening in vessels of pyelonephritic areas, but in addition there are fibrinoid necroses in the arterioles of both scarred and non-scarred areas.

Kidney removed post mortem. *Macroscopic:* size $11.5 \times 6.6 \times 4.5$ cm.; weight 210 gm. The surface is covered with yellowish nodules 2.5 mm. in diameter. The cut surface has a uniform mottled appearance. No dilatation of pelvis and calyces. *Microscopic:* typical kidney of malignant hypertension. Necroses present in glomeruli and arterioles. There are a few patches of lymphocytes, but no other changes suggestive of pyelonephritis.

Case 8. G. N., a boy born in 1936, was admitted to the National Hospital, Queen Square, on May 30, 1946, complaining of blurred vision for five days. Both parents were aged 36 years and were well. Examination of the fundi showed bilateral papilloedema, with a macular star and large soft exudates on the left side. No other signs were found in the central nervous system, and ventriculogram and electroencephalogram were normal. The systolic blood-pressure varied between 170 and 190. The urine showed no albumin and few leucocytes. The blood-urea was 31 mg. per 100 ml.; the urea clearance was 86 per cent. of normal. An intravenous pyelogram showed a large left kidney with good excretion and normal pelvis and ureter, but no excretion from the right kidney. He was transferred to St. Mary's Hospital on August 8, 1946. The blood-pressure varied between 170/130 and 186/140. The urine showed a trace of albumin; culture was sterile. Urea concentration was 4.2 per cent. On August 1, 1946 the right kidney and right adrenal were removed. The blood-pressure fell to 116/70, but rose slowly to 152/118 on August 29, 1946, when he was discharged. He was readmitted on November 22, 1946, free of symptoms. The fundi still showed papilloedema, and a few exudates about the left macula. The urine contained no albumin. Urea concentration was 3.4 per cent. The blood-pressure varied between 150/115 and 160/125. On December 12, 1946 three-quarters of the left adrenal was removed. He received pre-operative and post-operative treatment with eucortone and deoxycorticosterone acetate. After operation his blood-pressure varied between 140/110 and 150/120. He showed no signs of adrenal insufficiency when supporting therapy was withdrawn. In December 1947 the blood-pressure was 154/112, and papilloedema had nearly disappeared. He was last seen on August 22, 1951, aged 15 years; height 5 ft. 8 in., weight 8 stone; his blood-pressure was 165/118; the urine showed no albumin or cells; the urea concentration was 2.5 per cent.; the fundi showed no papilloedema and no exudates, and the left inferior nasal artery showed pronounced sheathing.

Examination of kidney. *Macroscopic:* right kidney 11 cm. long, with dilated calyces, and thinned parenchyma reduced to 0.2 cm. in places and nowhere more than 1 cm. thick. Surface relatively smooth. *Microscopic:* hydronephrosis with patchy chronic pyelonephritis. Vascular changes not so pronounced as in

other cases, consisting of moderate medial thickening of arterioles and small arteries, and some intimal proliferation of the latter.

Microscopy of right and left adrenals. Some medial hypertrophy of periadrenal vessels, but no other changes.

Left renal biopsy. No significant vascular lesions.

Case 9. W. H., a clerk, born in 1903, was admitted to St. Mary's Hospital in September 1949, because of three days' haematuria and two months' morning headache. His mother was 74 and his father 63 years of age, both being well. He had three sisters and one brother alive and well. On examination the blood-pressure was 230/140. The heart was moderately enlarged. The fundi showed no papilloedema, but some exudates round the right disk. The blood-urea was 35 mg. per 100 ml. The urine showed albumin, a few leucocytes and red blood-cells, and a scanty growth of faecal streptococci. An intravenous pyelogram showed a normal left kidney, and no excretion from the right kidney; a retrograde pyelogram showed gross pyelectasis in a congenitally abnormal right kidney. On September 19, 1949 the right kidney was removed. After operation the blood-pressure varied between 190 and 200 systolic and between 110 and 130 diastolic. The urine continued to contain albumin. He was last seen in December 1949, when his blood-pressure was 210/140.

Examination of kidney. *Macroscopic:* right kidney $9 \times 7.5 \times 4.5$ cm., of which a large part is dilated pelvis. There is an aberrant artery entering the lower pole. The kidney tissue is reduced to 0.5 cm. in places. *Microscopic:* chronic pyelonephritis. Fibrinoid necroses are present in the vessels of the non-scared areas; the glomeruli in these areas show necroses, cellular proliferation, and crescent formation. Fine intimal proliferation is seen in the arteries and larger arterioles of the scarred areas, and elastosis is present in the larger vessels. No necroses are present in these areas.

Case 10. G. L., a nurse, born in 1921, had an operation for acute appendicitis in November 1940; the surgeon noticed that the intra-abdominal arteries looked thickened. The blood-pressure was 210/125. The fundus showed no neuro-retinopathy. Between February and March 1941 the blood-pressure ranged from 220/130 to 230/150. The blood-urea was 32 mg. per 100 ml.; urea clearance was 95 per cent. of normal. The urine contained no albumin, and a few pus cells. An intravenous pyelogram showed a right kidney with double pelvis and ureter, and normal calyces; the left kidney was excreting poorly. On cystoscopy the bladder appeared normal; dye was excreted from the right ureteric orifice in four minutes; from the left there was feeble excretion after 15 minutes. On March 28, 1941 the left kidney was excised. The blood-pressure fell to 170/110 on April 2, 1941, and remained between 140/90 and 170/105 from then until 1944 during frequent examinations. The urine showed no albumin or deposit. The blood-urea was 24 mg. per 100 ml.; urea clearance was 66 per cent. of normal. In 1946, when she was six weeks pregnant, her blood-pressure was 210/100; the blood-urea was 29 mg. per 100 ml., urea concentration 3.15 per cent., and urea clearance 112 per cent. of normal; the urine showed no albumin or cells. Her blood-pressure settled to 144/68 with rest, but the pregnancy was terminated at the 14th week. On September 16, 1946 her blood-pressure was 175/100. In July 1951 she had a subarachnoid haemorrhage with hemiplegia; the blood-urea was 47 mg. per 100 ml., urea concentration 2.6 per cent., and blood-pressure 140/80. The urine showed no albumin, and an occasional white blood-cell.

Examination of kidney. *Macroscopic:* kidney $6 \times 3 \times 2.5$ cm. The surface is coarsely scarred. Two ureters are present, one draining the upper calyx

which is dilated, the kidney substance being reduced to 0·2 cm. The other ureter drains the rest of the kidney, the pelvis and calyces being dilated, and the parenchyma varying from 0·3 cm. to 1·0 cm. in thickness. *Microscopic*: scarred areas are separated from each other by relatively normal areas. The scars extend from beneath the capsule to the medulla, and consist of fibrous tissue infiltrated with lymphocytes. Glomeruli are considerably reduced in numbers, and the few that remain are hyalinized and degenerate. Tubules are somewhat dilated, are lined by flattened epithelium, and contain eosinophilic casts. Vascular changes in these areas consist of intimal and medial thickening of arterioles, without hyalinization, and fine intimal and medial thickening of the arteries. The intimal thickening consists of fine fibrous tissue, and is often cellular. We have used the term productive endarteritis for this change. Elastic reduplication is seen in small and medium-sized arteries. In the non-scarred areas the arteries show minor degrees of intimal and medial thickening. Other components are within normal limits. The pelvis is thickened, and beneath it are numerous lymphocytes.

Case 11. E. B., a meter-reader, born in 1912, noticed failing vision in December 1945. In 1932 he had a haemoptysis, and was treated with artificial pneumothorax. He had had a left and right orchidectomy in 1932 and 1937 for tuberculous epididymitis. His father died aged 69 years after gastrectomy; his mother died 12 hours after a fit; he had four brothers and one sister alive and well. Examination showed a eunuchoid appearance. The blood-pressure was 226/148. The fundi showed bilateral hypertensive neuro-retinopathy. The blood-pressure varied between 220/148 and 240/170. The blood-urea was 37 mg. per 100 ml.; urea concentration was 2·6 per cent. The urine contained albumin, and no tubercle bacilli. An intravenous pyelogram showed an enlarged left kidney, with normal excretion, and no excretion from the right kidney. On February 25, 1946 the right kidney, the right splanchnic nerves, the right first and second lumbar ganglia, and the right adrenal gland were excised. After operation the blood-pressure settled to between 150 and 170 systolic and between 100 and 120 diastolic. The blood-urea was 30 mg. per 100 ml. Urea concentration was 3·6 per cent. The fundus cleared rapidly, the papilloedema and large exudates disappearing in three months, and the star figure in one year. He was last seen in August 1951, when he was well and at work. The blood-pressure was 160/110, the fundi were normal, and the urine contained no albumin and no cells.

Examination of kidney. *Macroscopic*: right kidney $7 \times 4 \times 2\cdot5$ cm. Surface coarsely scarred. Pelvis and calyces dilated. Maximum thickness of renal parenchyma 1·2 cm. *Microscopic*: chronic pyelonephritis. Vascular lesions are extreme, and fibrinoid necroses are present (Plate 2, Fig. 5) in the scarred and non-scarred areas and deep to the pelvis. Other vascular changes are fine intimal fibrosis and some medial thickening, particularly in the pyelonephritic areas. There is elastosis of arteries of all sizes.

Microscopy of adrenal: vessels in the periadrenal fat have thickened media. Several small arterioles under the capsule show fibrinoid necrosis.

Cases 3 and 11 have been published as *Cases 3 and 1* by Pickering, Wright, and Heptinstall (1952).

Summary

Eleven patients are reported in whom one kidney was excised for the relief of hypertension. Their progress was followed for periods varying up to 10 years.

In one patient the excised kidney was tuberculous; hypertension was unaffected.

In 10 patients the excised kidney was reduced in size, and showed varying degrees of hydronephrosis and chronic atrophic pyelonephritis; in two patients, in whom an aberrant artery had previously been tied, the corresponding renal pole was atrophic. One patient died of a pulmonary embolus on the 10th day. In three patients with proved bilateral pyelonephritis, hypertension was not reduced by nephrectomy. Of six patients who showed no clinical evidence of bilateral disease, excision of the pyelonephritic kidney produced a gross fall of arterial pressure persisting for at least five years in one patient, and for 10 years in two; in one of the successful cases the hypertension was in the malignant phase. In the remaining three nephrectomy did not influence hypertension; in spite of the absence of clinical evidence bilateral disease cannot be excluded in these three cases.

The successful cases, and similar cases described by others, provide the only unequivocal evidence that a renal lesion can cause hypertension in man.

Hypertension in the malignant phase was unaffected by nephrectomy in one bilateral and two unilateral cases of pyelonephritis.

The malignant phase of hypertension was relieved by subtotal adrenalectomy in two patients in whom it had not been relieved by nephrectomy (Cases 3 and 8), and by subtotal adrenalectomy and subdiaphragmatic sympathectomy in one patient with malignant hypertension and bilateral pyelonephritis, who was not subjected to nephrectomy and is not included in this series; all these three patients were children. Subtotal adrenalectomy has not proved successful in adults with malignant hypertension not due to pyelonephritis.

In the six patients in whom hypertension has been reduced by nephrectomy or by subtotal adrenalectomy or by both, the arterial pressure has remained, for periods up to 10 years, persistently slightly or considerably above the normal level.

ADDENDUM

Since this paper was written we have had one more patient in whom one kidney was removed for the relief of hypertension with a successful result. Our final figures regarding unilateral pyelonephritis thus show material reduction of hypertension, by removal of the affected kidney, in four out of seven cases. The case report is as follows:

Case 12. D.B., a man aged 45 years, suddenly developed a severe headache, lost consciousness, and had a convulsion, in August 1951. He was admitted to the National Hospital, Queen Square, in status epilepticus; he regained consciousness four days after the onset. Investigation showed no evidence of a cerebral tumour, apart from raised pressure in the cerebrospinal fluid. He had gross hypertension, and an intravenous pyelogram showed that the left kidney was not excreting. He was admitted to St. Mary's Hospital on December 4, 1951, and stated that in the past three months he had had attacks of pain starting in the left loin and radiating to the left groin. On one occasion he had passed blood in his urine. His arterial pressure varied between 190 and 220 systolic

and between 120 and 140 diastolic. Papilloedema was absent, but in the left eye there were two large soft exudates typical of the early stage of hypertensive neuro-retinopathy. The blood-urea was 34 mg. per 100 ml. Urea concentration reached 2·1 per cent. The urine contained albumin, leucocytes, red cells, and a few granular casts, and was sterile on culture. An intravenous pyelogram showed a normal right kidney, but no excretion on the left side. On cystoscopy the left ureteric catheter met an obstruction at 1 cm.; urine from the right ureter contained a trace of albumin, but no cells. The left kidney was removed on December 17, 1951. The blood-pressure fell, and settled at 120/70 until his discharge on January 11, 1952. On April 9 the fundi showed no papilloedema or exudates, and the blood-pressure was 150/100. On April 30 the blood-pressure was 130/95. On July 29, 1952 the blood-pressure was 144/88; the urine contained no albumin, red cells, or casts, and only an occasional leucocyte. He had remained free from symptoms since operation, except attacks of chest pain at night, for which no cause was found.

Examination of kidney. *Macroscopic:* left kidney, $7.5 \times 5.0 \times 3.0$ cm., with 7 cm. of ureter. The capsule strips easily, leaving a smooth subcapsular surface. On the cut surface there is some reduction of parenchyma. The pelvis is not grossly dilated, and there are several small haemorrhages.

Microscopic: only two sections were examined. Areas of cellular infiltration, destruction of glomeruli, fibrosis, and atrophy of tubules are present, but are much less conspicuous than in any other kidney of the present series. The arteries all show medial hypertrophy; one shows cellular intimal thickening, but none shows necroses. In comparison with other kidneys of the series the changes are slight.

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FIG. 1. Kidney with dilated calyces and reduced parenchyma (Case 2). (Scale in centimetres)

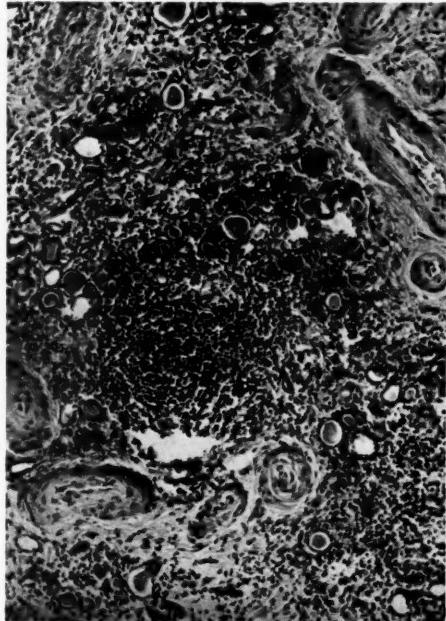


FIG. 2. Typical pyelonephritic area with disappearance of glomeruli, thickened vessels, and lymphocytic infiltration (haematoxylin and eosin, $\times 96$)

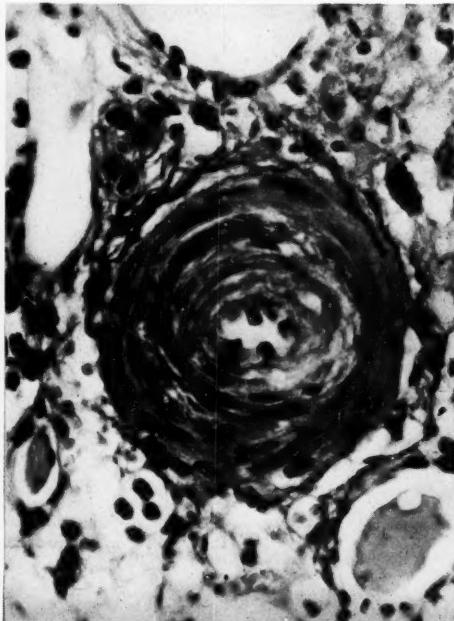


FIG. 3. Intimal proliferation in a small artery of the kidney (haematoxylin and van Gieson's stain, $\times 500$)

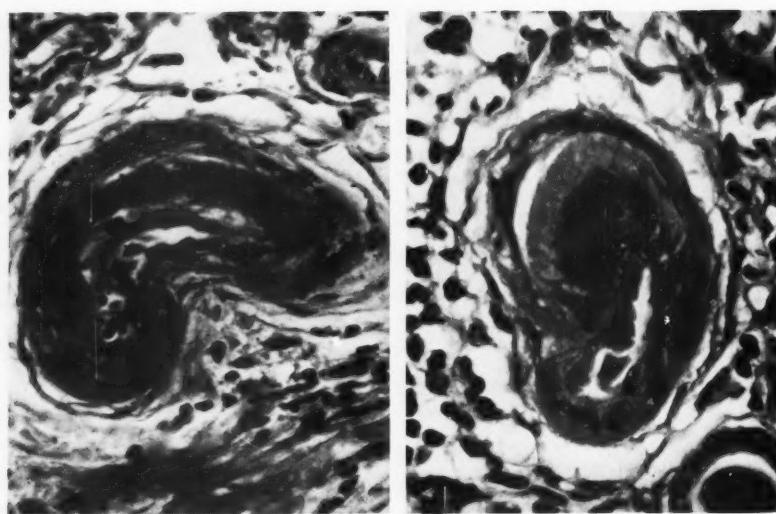


FIG. 4. Fibrinoid necrosis in kidney arteriole (Case 3) (haematoxylin and eosin, $\times 400$)

FIG. 5. Fibrinoid necrosis in kidney arteriole (Case 11) (haematoxylin and eosin, $\times 640$)



FIG. 6. Atrophic tubules containing eosinophilic casts in pyelonephritic area (haematoxylin and eosin, $\times 66$)

616.95-022.7 (Brucella)

CHRONIC BRUCELLOSIS¹

By GEOFFREY M. BARRETT and ANTHONY G. RICKARDS

(From the Departments of Medicine and Pathology, Royal Lancaster Infirmary)

With Plates 3 and 4

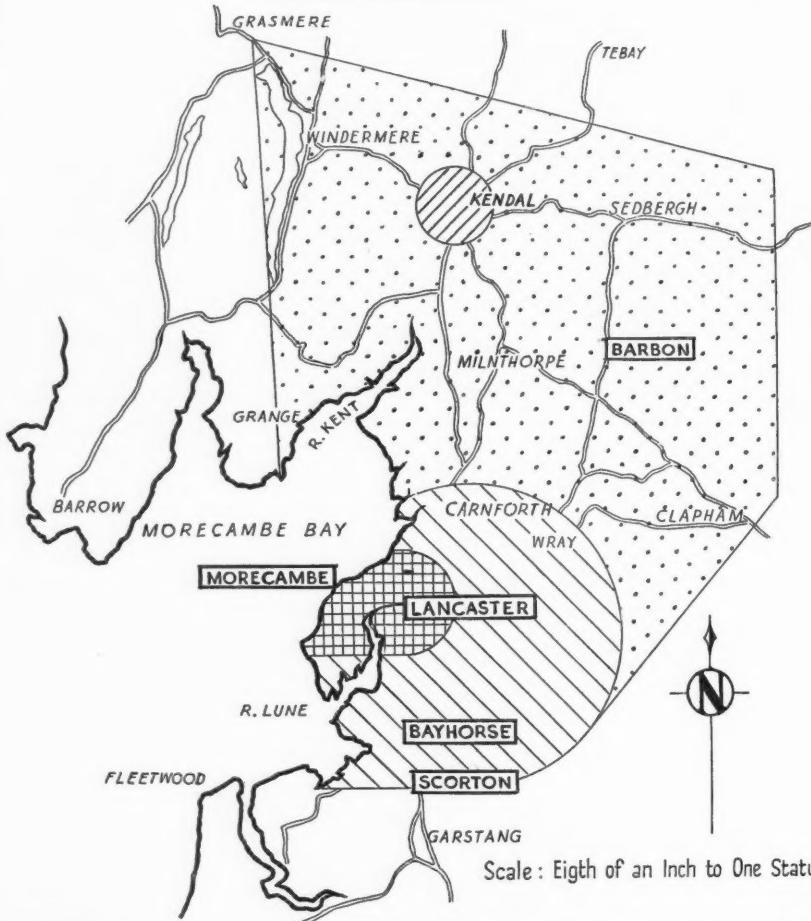
Introduction

It has been reliably estimated that 15 to 20 per cent. of adult bovine cattle in this country are infected with *Brucella abortus* (Dalrymple-Champneys, 1950). Though spread of infection to man is known to occur, its frequency cannot be accurately estimated since, unfortunately, Great Britain is one of the few countries where brucellosis is not compulsorily notifiable. Impressions of the incidence of infection are inaccurate owing to the general failure to appreciate that, apart from producing an acute pyrexial illness, the organism can evoke a granulomatous reaction in the tissues, leading to a state of chronic ill health with numerous though characteristic symptoms. In the United States, where much more interest is shown in the disease, about 4,000 cases of acute brucellosis are notified every year, and it has been estimated that there are 10 to 25 times as many cases of chronic infection. Brucellosis in an urban population is largely preventable by pasteurization of milk, and this fact alone may account for much of our national neglect of the disease, since most medical publications in Britain emanate from teaching hospitals situated in large towns and cities, where little raw milk is consumed. Certainly we know of no standard textbook of medicine or pathology published in Britain which gives an account of the symptomatology and histopathology of chronic brucellosis. It is probable that the extension of consultant services to the rural areas, which has been a feature of the National Health Service, will lead to a greater appreciation of the importance of brucella infections. It is the purpose of the present paper to draw attention to the syndrome of chronic brucellosis, and to evaluate the various diagnostic aids with special reference to aspiration liver biopsy.

Terminology. Brucellosis is the term used in the United States and Canada to describe human infection with brucella organisms. It is objected to by Dalrymple-Champneys (1950) on the grounds that it fails to draw attention to undulating pyrexia as a predominant symptom, and because of its application to 'the very different disease caused by Brucellae in animals'. We dislike the alternative description of undulant fever for the very reason that, at least in chronic infections, pyrexia is often absent, and when present is frequently not appreciated by the patient; moreover it seems probable that the fundamental histopathology of chronic brucella infection is the same in man as in animals.

¹ Received June 2, 1952.

MAP SHOWING CONSUMPTION OF HEAT TREATED
MILK IN THE AREA



Scale : Eighth of an Inch to One Statute Mile

1.		PERCENTAGE OF MILK CONSUMED WHICH IS HEAT TREATED - 60 to 65 %
2.		" " " " " " 20%
3.		" " " " " " 1 to 15 %
4.		" " " " " " 0 to 1 %

SITUATION OF PASTEURISING PLANTS SHOWN THUS - **LANCASTER**

NOTE :- IN AREAS SHADED AS IN 3 & 4 THE HEAT TREATED MILK IS MAINLY CONSUMED ON THE FRINGES OF TOWNS, OR IN SCHOOLS.

Findings in 25 Cases of Chronic Brucellosis

Case number	Age (years)	Occupation	Duration of disease	Symptoms		Signs		Investigations	
				Before skin test		After skin test		Histological appearance of liver biopsy specimen	
1	2	Housewife	4 y.	++	++	No	Yes	"	"
2	3	Farmer	3 y.	++	++	No	Yes	"	"
3	30	Plasterer	3 y.	++	++	No	No	"	"
4	33	Textile worker	8 y.	++	++	Yes	No	"	"
5	53	Cheese factor	8 y.	++	++	Yes	No	"	"
6	49	Male nurse	6 m.	++	++	Yes	No	"	"
7	7	Director	2 y.	++	++	Yes	No	"	"
8	51	Farmer's wife	4 y.	++	++	Yes	No	"	"
9	39	Tyre salesman	10 y.	++	++	Yes	No	"	"
10	56	Farmer	8 y.	++	++	Yes	No	"	"
11	37	Male nurse	5 y.	++	++	Yes	No	"	"
12	33	Engineer	5 y.	++	++	Yes	No	"	"
13	50	Labourer	3 y.	++	++	Yes	No	"	"
14	39	Farmer's wife	3 m.	++	++	Yes	No	"	"
15	62	Clerk	8 y.	++	++	Yes	No	"	"
16	44	Farmer	19 y.	++	++	Yes	No	"	"
17	40	Farmer	8 m.	++	++	Yes	No	"	"
18	47	Farmer	6 m.	++	++	Yes	No	"	"
19	56	Farmer	8 y.	++	++	Yes	No	"	"
20	55	Housewife	10 y.	++	++	Yes	No	"	"
21	43	Farmer	15 y.	++	++	Yes	No	"	"
22	45	Vet. surgeon	15 y.	++	++	Yes	No	"	"
23	26	Farmer	9 m.	++	++	Yes	No	"	"
24	21	Farmer	1 y.	++	++	Yes	No	"	"
25	30	Farmer	1 y.	++	++	Yes	No	"	"

In the present paper we are restricting our attention to chronic brucellosis, and we include under that heading all cases in which symptoms have been present for three months or more.

The Present Investigation

Our description of chronic brucellosis is based on 25 personally studied cases, which form part of a series of 62 brucella infections diagnosed in this area during a period of 18 months. The district is essentially agricultural, with a total population of approximately 170,000; its geographical confines are shown in the Map. Facilities for heat-treatment of milk are available throughout the area, and have a daily capacity far in excess of the total milk consumed. Unfortunately, as in other rural areas, there is considerable prejudice against the use of pasteurized milk, which except in the main centres of population forms a negligible proportion of the total milk consumed.

Clinical features

The main findings in the 25 cases are set out in the Table.

Sex incidence. It will be seen that 21 of the patients were male and only four female. This sex difference has been noted by other workers in large series of cases (Magoffin, Kabler, Spink, and Fleming, 1949; Taylor, Lisonne, Vidal, and Hazemann, 1938; Olin, 1935; Dalrymple-Champneys, 1950). The latter author considered that the difference could not be explained simply by the occupational risk of direct infection, and certainly in our small series this explanation seems inadequate, as only 12 of the male patients had direct contact with cows or untreated dairy products.

Age incidence. No conclusion can be drawn from such a small series, but it is of interest that there were nearly twice as many patients in the 40-to-59-years as in the 20-to-39-years age-group.

Occupation. The fact that 14 of the 25 patients were directly connected either with farms or with the marketing of dairy products is clearly of importance. Though these patients had all consumed raw milk, they were in addition exposed to the risk of direct infection. We have encountered other interesting cases of direct infection; thus a plumber and his son both developed brucellosis within a few weeks of working on shippons at a farm where there had been a number of cases of contagious abortion. Such cases present a problem in preventive medicine which can only be solved by the eradication of bovine infection. The problem is nationally important, since chronic brucellosis in farmers must be responsible for much low-grade ill health which, by reducing efficiency and work potential, will adversely affect the output of dairy products.

Associated diseases. Three patients suffered from radiologically proved chronic duodenal ulceration; all had been treated with milk diets, but all were also exposed to the risk of direct infection. One of these patients developed a high, though largely symptomless, pyrexia following partial gastrectomy. Another patient dated the onset of her symptoms to the extraction of a number of teeth, and a third (not included in the present series) developed an unexplained

pyrexia after an operation for strangulated hernia. It is generally agreed that surgical operations or battle wounds may be followed by acute symptoms of malaria in chronically infected patients, and it seems possible that the same may apply in chronic brucellosis. The diagnosis should clearly be considered when investigating an unexplained post-operative or puerperal pyrexia, especially in a rural area. Case 23 showed an interesting association of chronic brucellosis with infectious mononucleosis, which may be of significance in view of the present tendency to regard glandular fever as a hypersensitive response of the reticulo-endothelial system to a variety of infective stimuli. The patient, a farmer, had experienced attacks of pain in the right hypochondrium, and had had drenching night sweats for the preceding nine months; he tired easily, and often suffered from diffuse aches and pains in his limbs. At times he had thought he was losing the use of his left arm, and there had been neuritic pain in this limb. Admission to hospital followed a week of pyrexia, headache, sore throat, and increasing malaise. His temperature on admission was 101·6° F., and physical examination showed moderate superficial lymphadenopathy, with enlargement of the liver and spleen. The total white-cell count was 16,800 per c.mm., with 13,640 lymphocytes; the Paul-Bunnell test was positive at a titre of 1/448 (after absorption with guinea-pig tissue 1/224) and *Br. abortus* agglutinins were present at a titre of 1/120. One week later the *Br. abortus* titre was nil, but after a further month it had again risen to 1/120, at which time the heterophile antibody titre was 1/16. Brucellin skin-testing was performed with a strongly positive result, and the brucella antibody titre subsequently rose to 1/640.

Symptomatology. Few sufferers from chronic brucellosis appear really ill, yet characteristically they complain of a number of symptoms of apparent severity. This association of severe symptoms and an appearance of well-being often suggests a psychosomatic disturbance; many such patients are regarded as neurotic, and not a few find themselves referred to psychiatric clinics. The six symptoms encountered most commonly were sweating, lassitude, chills or rigors, joint pains, diffuse rheumatism, and gastro-intestinal disturbances; of these sweating and diffuse rheumatism were by far the most constant (see Table). Sweating usually took place at night, and was comparable in degree to the drenching night sweats of tuberculosis. Lassitude and weakness, though sometimes continuous over periods of months, were more often intermittent; when present they were most severe towards the end of the day. Frequently the patients stated that they felt perfectly well in the morning, managing a few hours of good work, only to tire and become irritable as the day progressed. There was not in these patients the rapid alternation of mood characteristic of the cyclothymic neurotic. Chills and rigors were experienced at some time by 13 of the 25 patients; they occurred at various times of the day, and did not appear to be related to the presence or absence of pyrexia. A number of patients experienced frequent chills at times when they showed no elevation of temperature, and conversely one patient (Case 17) had an afternoon temperature between 103° and 104° F. for several weeks without experiencing any chills or rigors. This patient continued to work on his farm throughout this

period, and refused to regard himself as being ill. Pain in some form occurred in all cases; characteristically it affected the muscles and, although mild in degree, was widespread and usually associated with stiffness, most pronounced on rising in the morning. In some cases the pain was localized to the joints, and was severe enough to suggest a diagnosis of acute rheumatism or rheumatoid arthritis. Nine patients in the present series had received physiotherapy, sometimes of prolonged duration, and although some had benefited temporarily none had achieved permanent relief. Muscle pain seemed often to be localized to the pectoral group, and two patients were referred with a suggested diagnosis of angina pectoris. Pain was sometimes described as neuritic, and in these cases paraesthesiae also occurred; four patients stated that they had suffered from frequent attacks of lumbago and sciatica, but none showed objective evidence of neurological involvement. Headaches were described by seven patients in the series and, though often generalized, tended to be localized to the occipital region. Of the gastro-intestinal disturbances, which occurred in 11 cases, anorexia, abdominal pain, and constipation were predominant. A number of patients who did not originally admit to constipation commented on their improved bowel action after treatment. Cholecystectomy had been performed in one case, and appendicectomy in two others, without relief of symptoms.

Apart from the more constant symptoms that have been described, it was not unusual to find evidence pointing to the involvement of other systems. Symptoms referable to the respiratory tract were described by two patients. The first, a farmer aged 24 years, had been unwell during the preceding 12 months. He complained of malaise, headaches, diffuse rheumatism, and back-ache. One month before he was referred to hospital he had had pyrexia, a cough, and pleural pain on both sides of his chest. From the beginning of the fever and cough the sputum had contained considerable quantities of fresh blood, and this persisted for two weeks, the blood gradually becoming darker. There had been a similar episode six months previously. X-ray examination showed only a slight shadowing in the right lower lobe; a bronchogram was normal, and the Mantoux test was negative. Brucella agglutinins were present at a titre of 1/20, but two weeks after a strongly positive brucellin skin test the titre had risen to 1/160. A course of combined aureomycin and streptomycin led to complete and lasting symptomatic improvement and a clearing of the X-ray picture. A similar story of repeated haemoptyses has been encountered in other cases of chronic brucellosis. The second case, a milk roundsman with bronchial asthma of five years' duration, was referred for skin-testing preliminary to possible desensitization, but there was no reaction to the usual group-allergens. A history of nocturnal sweating and diffuse rheumatism was obtained, and a brucellin skin test was strongly positive. Subsequent antibiotic treatment led to a complete cessation of asthmatic attacks. Involvement of the renal tract occurred in one of our patients (Case 20), a housewife aged 55 years, who was referred for consultation with a suggested diagnosis of neurosis and hypochondriasis of 10 years' duration. Previously she had been a bright, cheerful, and energetic woman. Complaints during the 10 years

included severe nocturnal sweating, undue fatigue, diffuse rheumatism, and severe constipation. More recently there had been dizziness, minor syncopal attacks, and paraesthesiae in the hands. Nine years earlier there had been an episode of haematuria, and this had recurred on four further occasions, the last being seven months before consultation. Dysuria accompanied the haematuria, and at various times she had had frequency of micturition which sometimes amounted to 20 times a day. Urinary infection had never been demonstrated, intravenous pyelography had shown no abnormality, and cystoscopy on three occasions had shown no bladder disease. Retrograde pyelography had twice been performed with normal results. Physical examination showed no abnormality other than moderate enlargement and slight tenderness of the liver. Serum agglutinations for *Br. abortus* were negative, but a skin test was very strongly positive with marked pseudopodia formation, and two weeks later agglutinins were present at a titre of 1/640. The response to treatment has further strengthened the diagnosis of chronic brucellosis in this case.

Involvement of the skin from contact-infection occurred in a veterinary surgeon (Case 22), who had worked in the area for many years, and had had periods of malaise which he himself attributed to brucellosis. These episodes were marked by low-grade fever, night sweats, severe backache, and generalized muscle pains. He stated that as a student he had had 'positive agglutinations' for *Br. abortus*. For six years roughening of the skin and warty excrescences had been present on the palmar and dorsal surfaces of both hands. Various diagnoses and treatments had been suggested. Two years before we saw the patient a biopsy had been performed; the section showed an area of hyperplastic squamous epithelium overlying a dermis markedly infiltrated with chronic inflammatory cells, some of which were arranged in the form of non-caseating granulomata (Plate 4, Fig. 5). A diagnosis of warty lupus was made, and treatment with calciferol was given. The response to therapy was negligible, and the patient's worries were increased by a sensitization dermatitis, the severity of which virtually prevented him from performing rectal or vaginal examinations on cows. During the same period episodes of lassitude and malaise became increasingly severe and frequent. After consultation a course of aureomycin, with intravenous injections of typhoid-paratyphoid vaccine, was advised; on the day following the second protein-shock therapy the patient collapsed with what he described as an extreme accentuation of all his previous symptoms; he became covered with a profuse skin eruption similar to his previous sensitization dermatitis. After this 'Hershheimer' reaction the patient made steady progress, and finally showed marked subjective improvement. On the fourth day of treatment it was noticed that the warty skin lesions had largely resolved, and at the end of treatment they could only be detected as a violaceous staining of the skin. Four months after treatment there was a minor recurrence of general symptoms, and thickening of the skin was again apparent in one area. On reviewing this case it was considered probable that the original diagnosis of cutaneous tuberculosis was wrong, and that the granulomatous lesions were due to brucellosis.

Physical examination. The information to be gained from physical examination of the patient can never be diagnostic of chronic brucellosis, but may support an otherwise doubtful history. In particular there should be careful palpation for enlargement of the liver and spleen. Analysis of the details given in the Table shows how frequently one or both of these viscera are palpable:

Enlargement of:	Liver	Spleen	Liver or spleen	Neither
Number of cases:	15	9	20	5

When the liver edge was palpable below the costal margin it was usually found to be moderately tender; splenic tenderness was never elicited. Hepatic enlargement was never gross, averaging 3 to 4 cm. in full inspiration. Enlargement of the axillary lymph-nodes was found in three patients but, as they were manual workers, no particular significance was attached to this finding. In spite of the frequency of arthralgia, no patient showed swelling, local heat, redness, or limitation of movement of an affected joint. Of the 25 patients, 11 when admitted to hospital were found to have a low-grade pyrexia, but in no case did the maximum temperature exceed 99.6° F.

Laboratory and special investigations

1. White- and red-cell counts, haemoglobin estimations, and blood sedimentation rates were done in all cases, but provided no information of diagnostic value. White-cell counts tended to be below normal, and there was often a lymphocytosis; erythrocyte sedimentation rates were sometimes high, but were usually within normal limits.
2. The brucellin intradermal reaction was positive in all the cases described. The standard technique adopted involved the injection of 0.1 ml. of the antigen into the skin of the forearm, and subsequent inspection at 24-hour and 48-hour intervals. A delayed reaction appeared in one case, the maximum flare occurring five days after the injection, but in general there was little extension of the local lesion after 24 hours. There appeared to be two distinct types of local response to brucellin, some patients showing an area of erythema slightly elevated above the surrounding skin, and others showing a definite induration with a centre which might become haemorrhagic or necrotic. Occasionally these two types of lesion coexisted. The weakest reaction accepted as positive was an area of erythema 3 cm. in diameter or an area of induration 2 cm. in diameter.
3. Serum agglutinations were tested by a standard technique, with samples of blood withdrawn at the time of skin testing. In some cases agglutination reactions were repeated two weeks after brucellin injection. The values obtained are shown in the Table.
4. Blood cultures were made on a variety of media, but in no case was a brucella organism isolated.
5. Aspiration liver biopsy was performed with the technique described by Sherlock (1945), and 12 patients in the present series were subjected to the examination. In each case there was an abnormal histological appearance,

though in some instances step sections at intervals of 50 μ had to be cut from the whole block before lesions were detected. The most characteristic lesion was a nodular granuloma, resembling a non-caseating miliary tubercle, found anywhere within the liver parenchyma, and not related to portal tracts or to specific zones of the liver lobule. The size of these lesions varied from 100 to 180 μ in diameter. Most lesions were clearly delineated from the adjacent liver tissue, though not surrounded by any clear limiting sheath, but other lesions were less circumscribed, and blended indefinitely into the surrounding tissue. The cells comprising the lesions were predominantly of epithelioid type, though eosinophils, lymphocytes, plasma cells, and occasionally polymorphonuclear cells might be present. Giant cells were sometimes found. The interstitial tissue was composed of a fibrous network giving a positive reaction for reticulin with silver stains. We have attempted to demonstrate micro-organisms within the lesions, but have not been successful. In two patients (Cases 7 and 9) the histological lesions consisted of focal infiltrations of lymphocytes into portal tracts, without the distinctive nodular granulomata. In view of the clinical histories and other findings in these cases this infiltration, although not specific, probably resulted from systemic infection with brucella organisms. Plate 3 (Figs. 1, 2) shows the typical histological features of the hepatic granulomata.

Discussion

As long ago as 1912 Fabyan recognized the intracellular parasitism of the organisms, and revealed their tendency to live and multiply in non-phagocytic cells, particularly in the renal epithelium and liver-cells of guinea-pigs. Since Fabyan's original communication the characteristic histological changes have been reported in various animals, notably in guinea-pigs by Jaffé (1922), Cotton (1922), Meyer, Shaw, and Fleischner (1922), Smith (1926), and Braude (1951a); in mice by Feldman and Olson (1935); in monkeys by Huddleson and Hallman (1929); in dogs by Margolis, Forbus, and Kerby (1945); and in rats and rabbits by Nyka (1948). We have been able to confirm the findings of previous workers in the production of nodular granulomata in the spleens of guinea-pigs after intraperitoneal injection of a suspension of *Br. abortus* (Plate 4, Fig. 3). Recently, through the courtesy of Mr. J. Brennan, a veterinary surgeon, we were able to examine *post mortem* two cows slaughtered on account of infection with *Br. melitensis*. Both animals had aborted within the preceding four months, and although we were unable to demonstrate any histological abnormality in the uterine mucosae, they both had scanty hepatic granulomata (Plate 4, Fig. 4). Granulomata were first demonstrated in human material by Löffler and von Albertini in 1930, and later von Albertini and Lieberherr (1937) detailed the changes occurring in the liver and spleen. Within recent years Hoffbauer and Spink (1947) first reported the distinctive hepatic lesions as revealed by liver biopsy in human beings. These findings have since been confirmed by other workers (Spink, Hoffbauer, Walker, and Green, 1949), and it has now been proved beyond doubt that, in the majority of cases of brucellosis, the liver will be found to contain these highly distinctive granulomata.

Little information is available concerning the eventual fate of the hepatic lesions in man. The possible evolution of chronic hepatic brucellosis into portal cirrhosis was first postulated by Schittenhelm (1932). Since his report several authors have reported on this association (Wohlwill, 1932; Rothenberg, 1933; Diehl and Roth, 1935; McCoy, 1935; Hantschmann, 1936; Chaikin and Schwimmer, 1943; Abellan Ayala, 1945; Pedro Pons, Bacardi Noguera, and Alvarez Zamora, 1945; Cohen, 1946; Spink, 1948). Mettier and Kerr (1934) produced histological evidence of an associated hepatitis in brucellosis, and Hoffbauer and Spink (1947) reported a variable increase in portal connective tissue revealed by liver biopsy. Hoffbauer (1946) cited two patients who suffered from proved brucellosis and later developed typical portal cirrhosis, confirmed either at autopsy or by liver biopsy. More recently McCullough and Eisele (1951) have recorded a well-documented case of chronic brucellosis in a man of 52 years of age. Initial liver biopsies showed typical brucella granulomata, with areas of focal necrosis and cellular infiltration into portal tracts. Serum-agglutinins were present to a titre of 1/640, and *Br. abortus* was grown from the biopsy specimen. A second biopsy specimen, taken during an operation for surgical repair of an abdominal hernia, showed widespread nodular hyperplasia. The naked-eye appearance of the liver supported the diagnosis of portal cirrhosis. No information is available in the literature as to the appearance of the hepatic granulomata in man after treatment with the newer antibiotics. We were therefore fortunate in securing the co-operation of one of our patients (Case 3), who consented to a second liver biopsy 19 days after the original aspiration, which had revealed multiple nodular lesions. During the interval he received a 14-day course of aureomycin (4 gm. daily). At the end of this course of treatment liver biopsy disclosed no histopathological lesions of any type. In spite of the disappearance of lesions, this patient relapsed some months later. The evolution of the characteristic hepatic nodule has recently been studied in animals by Braude (1951b). Using guinea-pigs and mice as experimental animals, and sacrificing them at various intervals after intraperitoneal injection of brucella organisms, he was able to demonstrate that within six hours after infection parasitized polymorphs were collected into focal aggregations, in which one or more Kupffer cells were included. Within 72 hours polymorphs had disappeared, and their place was taken by aggregates of Kupffer cells, and at the end of 120 hours these aggregations had become typical nodular granulomata. Guinea-pigs sacrificed one year after infection showed no liver lesions.

The lesions in man, while highly characteristic, are not specific. The hepatic granulomata in Boeck's sarcoidosis show a very close resemblance to those of brucella origin, although Gormsen (1948) maintained that the lesions of brucellosis are usually smaller and less distinctly limited than those of sarcoidosis. He also maintained that the epithelioid cells are less rich in protoplasm and seldom show giant-cell formation. We have not been able to study enough cases of other forms of sarcoidosis to evaluate these differences thoroughly, but in those we have studied the hepatic granulomata have been very similar to

those seen in brucellosis. We use the term 'other forms of sarcoidosis' to emphasize the similarity of the tissue-reactions to the brucella antigen and to the antigens held responsible for the clinical and pathological syndrome of sarcoidosis. It is becoming widely recognized that the term sarcoidosis embraces several distinct disease entities, which are united only in exciting a similar non-specific tissue-reaction to their various antigens. Scadding (1950) suggested that sarcoidosis should be classified as far as possible on an aetiological basis, and spoke, for example, of tuberculous sarcoidosis and beryllium sarcoidosis. Among bacterial antigens he mentioned brucellae as a cause of widespread granulomata of sarcoid type. Apart from Boeck's sarcoidosis, liver granulomata may be found in cases of erythema nodosum; van Beek and Haex (1948) demonstrated typical hepatic nodular granulomata in eight of ten cases examined. The skin eruption was apparently of tuberculous origin. Their illustrations show granulomata indistinguishable from those which we describe as occurring in brucellosis. Hepatic granulomata have also been described in infectious mononucleosis. In this condition differentiation is made easy by the marked portal infiltration combined with Kupffer-cell hyperplasia. The nodules are described as being composed of islets of lymphocytes (Bertrand, 1949; Custer and Smith, 1948). It is more than likely that other, as yet undetermined, agents can elicit the sarcoid reaction, and their discovery will be hastened by the more general realization that the pathological syndrome of sarcoidosis can be produced by several different stimuli. Any investigations undertaken in a case of sarcoidosis should include a search for brucella organisms or their antibodies. It is apparent that the nodular lesions of brucellosis closely resemble the histological changes seen in other forms of sarcoidosis, and if differences exist we doubt if they are pronounced enough to determine the diagnosis in any particular case. The difficulties in differentiating between the different forms of sarcoidosis on histological grounds are well exemplified in the case history of a patient who was admitted under our care during 1951.

A farmer, 43 years of age, was admitted to the Royal Lancaster Infirmary on February 17, 1951. He gave a history of typical thrombophlebitis of his left calf, with swelling of the foot which began about four months before admission. One month later this was followed by sudden pain in his left chest. He was confined to bed by his family doctor for six weeks, during which his temperature was raised. A fortnight before admission he had improved sufficiently to be allowed out of bed. One week later he noticed that he was coughing up spots of blood, and on the day of admission he had a sudden pain in his right chest. On admission the left foot and ankle were found to be swollen. During his nine days in hospital he had a high temperature, in spite of penicillin therapy, and after further episodes of haemoptysis he collapsed and died on February 26, 1951. Autopsy was performed on the day of death. The significant lesions found included a large pulmonary embolus. Ante-mortem thrombus was present in the lower third of the inferior vena cava, and extended down both femoral veins. Both lungs showed extensive infarcted areas of varying age, and the hilar lymph-nodes were much enlarged. No other significant lesions were noted on macroscopic examination. Histological study of the lymph-nodes showed replacement by non-caseating nodular granulomata of sarcoid type. Similar

histological features were present in the liver and spleen. These lesions were indistinguishable from the granulomata of brucella origin. Careful histological study of the thrombus and vein-walls showed no evidence of granulomata.

There are good grounds in this case for incriminating brucella organisms in the pathogenesis of the pulmonary embolus, for not only did the patient's occupation lead him into direct contact with cattle, but the acute nature of his illness makes other forms of sarcoidosis unlikely. This view is strengthened by the frequent references in the literature to infection of the vein-wall by brucella organisms. Thrombophlebitis of the splenic vein, with the formation of sub-intimal brucella granulomata, has been described by Rabson (1939), and Harris (1950b) has noted 'thrombophlebitis of deep and superficial veins associated with brucellosis in several patients'. Sprunt and McBryde (1936) quoted Wohlwill's report (1932) of the death of a woman from pulmonary embolus secondary to femoral thrombophlebitis of brucella origin, and Bagley, Mueller, and Wells (1936) described a further case of pulmonary embolus during the course of brucellosis. Unfortunately, the possibility of brucellosis in our patient was not considered until after autopsy, but the case is of interest in demonstrating the difficulty of separating the different forms of sarcoidosis on histological grounds.

From the diversity of symptoms and signs exhibited by these patients it is not surprising to find that the tissue-reactions in brucellosis are widespread, and that the lesions are not confined to the spleen, lymph-nodes, and liver. Sundberg and Spink (1947) and Gormsen (1948) were able to demonstrate granulomata in sternal-marrow aspirates in 19 of 31 cases of brucellosis. Endocardial lesions, macroscopically indistinguishable from those produced by *Streptococcus viridans*, have frequently been observed in brucellosis (Spink, Titrud, and Kabler, 1942; Olin, 1935; Rennie and Young, 1936; Hardy, Jordan, Borts, and Hardy, 1930; Voth, 1949; Beebe and Meneely, 1949). Harvey (1948) made a study of pulmonary brucellosis, and described a characteristic clinical course marked by perihilar lymphadenopathy and bronchitis or pneumonitis of prolonged duration, and usually followed by spontaneous subsidence with resorption or fibrosis. Involvement of the central nervous system seems to be not infrequent, and has been the subject of several papers (Spink and Hall, 1950; Nelson-Jones, 1951; Nichols, 1951). The last-named author described a case in which *Br. abortus* was recovered from the cerebrospinal fluid, and cited 22 other cases from the literature in which the diagnosis of cerebral brucellosis was confirmed by culture of the organisms from the cerebrospinal fluid or by direct culture of infected cerebral tissue at operation. Osteolytic lesions in bone have been described by some workers (Spink, 1948; Harris, 1949). When lesions of this type were localized in the vertebrae, they were often associated with symptoms suggestive of herniation of an intervertebral disk or spondylitis. Weed, Dahlin, Pugh, and Ivins (1952) have described some remarkable cases of bone and joint brucellosis, some of which had been diagnosed as tuberculous arthritis before culture of the infected tissues revealed their true nature. Other manifestations of brucellosis include a granulomatous arteritis with formation

of mycotic aneurysms. Two such cases, in which the lesions were situated in the basilar and femoral arteries, were followed by rupture (Hansmann and Schenken, 1932; De Gowin, Carter, and Borts, 1945). A chronic form of miliary peritonitis was reported by Amoss (1931), and a case of chronic granulomatous cholecystitis was described by Mettier and Kerr (1934). Haematuria has been described in two cases by Harris (1950d), and Forbus (1943) described a condition of focal granulomatous nephritis of brucella origin. Two further cases of urinary brucellosis, occurring in a farmer and a butcher, have recently been reported by Greene, Weed, and Albers (1952); both these cases presented symptoms closely resembling those seen in urinary tuberculosis. That the genital tract does not escape the lesions has been shown by several workers. Brucella salpingitis has been described by Harris (1950c), and chronic brucella epididymitis with sinus formation by Simpson (1930). Ocular manifestations of the disease have frequently been reported, and include uveitis, keratitis, and iritis (Woods and Guyton, 1944; Woods, 1946; Harris, 1943). Brucella dermatitis, an occupational lesion well known to veterinary surgeons, has been described by Flanchik and Freyfeld (1934), Lomholt (1946), and Harris (1950e). In most of these cases the diagnosis was established by isolation of the organism, and it would be no exaggeration to say that brucellosis competes with syphilis in the variety of its clinical manifestations.

Brucella skin antigen. In all our cases the brucellin skin test has been strongly positive. The intradermal test, which is more frequently employed as a diagnostic aid in the United States than in this country, was first used by Fleischner and Meyer (1917), who employed a killed whole-organism suspension of *Br. abortus*. Burnet (1922) made further studies with *Br. melitensis*, and later Giordano (1929) reported favourable results from the use of a heat-killed suspension of brucella cells in the detection of the disease. As early as 1913 McFadyean and Stockman had used the antigen as a diagnostic aid in the detection of the disease in cattle. Huddleson, in an attempt to counteract the sloughing properties of the whole-organism suspension, prepared an active protein-nucleate fraction of brucella cells which he named brucellergen (Huddleson, Hardy, Debono, and Giltner, 1939a), but experience has shown that this purified product is less sensitive than the whole-organism suspension (Hagebusch and Frei, 1941; Harris, 1950a). These authors described several cases of brucellosis, with positive agglutination reactions and blood cultures, in which skin reactions were negative to brucellergen and positive to the whole-organism suspension. Brucellin, the dermal antigen used in this country and prepared by the Central Public Health Laboratories, is a whole-organism suspension. Positive skin tests in themselves do not necessarily indicate current infection, although a negative skin test is strong evidence against active brucellosis. In a recent survey by Spink, Hall, and Aagaard (1946) it was found that 96 per cent. of persons with demonstrable antibodies reacted positively to the intradermal injection of a brucella antigen, and Braude, Gold, and Anderson (1949) confirmed this finding. In our experience the test has proved of value in cases in which a strong clinical history was associated with absence of serum-agglutinins. A positive reaction

without strong confirmatory clinical or pathological evidence should not be regarded as signifying current infection.

It has frequently been observed that injection of brucella antigen is followed by a rise in the titre of serum antibodies (Braude, 1948), and it is often insisted that diagnostic skin testing should be deferred until serum-antibodies have been titrated. Harding (1949) carried out a survey of 296 students when investigating this reaction. He found that approximately 20 per cent. of 53 persons who were previously free of antibodies developed them after diagnostic skin tests. Moreover, in many of these cases there was no skin-reaction to the intradermal injection. Further studies were made by Heathman (1934) and Goldstein (1934), who found that intradermal skin testing with a heat-killed suspension of brucella organisms stimulated the production of agglutinins in a large proportion of subjects. Goldstein (1934) maintained that when a fat-free antigen was used there was no agglutinin response. Other workers reported similar results after skin testing; Elton (1948) found remarkable elevation of antibody titres in eight laboratory workers after skin tests, and Bower and Chudnoff (1948) reported similar results. Elton was of opinion that the subsequent rise in antibody titre did not depend on the result of the skin test, but on the amount and type of antigen used. On the basis of reports of this nature, a rising titre after skin testing has been regarded as insignificant from the diagnostic point of view. It appeared to the present writers that an increase of serum-antibodies after negative skin testing was remarkable in itself, and accordingly we undertook a small-scale investigation of this problem. Fourteen healthy volunteers from the laboratory and medical staff, between the ages of 18 and 34 years, were employed in the investigation. None of the volunteers gave any history suggestive of brucellosis. Apart from experience in the armed forces, only one person (J. H.) had followed an occupation outside the hospital services. This man had been recently employed on a farm. Serum-agglutinins were first sought before any skin testing was done, and were uniformly absent except in the case of J. H., who showed a titre of 1/120. In addition to the usual agglutinins detectable in a saline medium, hereafter referred to as 'saline agglutinins', sera were examined for the presence of incomplete agglutinins by the use of a Coombs reagent (anti-human-globulin serum). Incomplete agglutinins were found only in the case of J. H. Skin testing was carried out immediately after venepuncture, 0·1 ml. brucellin being injected intradermally into the forearm of each of the 14 volunteers. Two subjects, K. W. and J. H., gave positive reactions reaching a maximum intensity within 48 hours. Of the two positive reactors, one (J. H.) had a positive saline titre, and one (K. W.) had no demonstrable saline agglutinins. Ten days later each volunteer was again given an intracutaneous dose of 0·1 ml. brucellin. A similar result was encountered, the previous reactors again showing a positive response, but rather less in intensity. Seventeen days later the procedure was again repeated, with the same result. Four months later a final intracutaneous injection was given. The results were unchanged except in one of us, who showed a weak positive reaction. During the course of the skin testing search was made on four occasions for evidence of

saline or incomplete agglutinins. In volunteers who gave repeated negative skin-reactions, and who showed no initial agglutinins, no subsequent saline or incomplete agglutinins were found in titres higher than 1/80, and in the majority there was no rise at all in agglutinin titre. In two subjects, however, there was a sharp rise in antibody titre. In K. W. and J. H., who both showed strong skin-reactions, the maximum titres of saline agglutinins rose from nil to 1/160 and from 1/120 to 1/960 respectively. Maximum titres occurred between two and three weeks after the intradermal injection.

The results of this investigation would seem to indicate that intracutaneous injection of brucellin in non-sensitized persons does not provoke a significant antibody response, and that a rise in titre of brucella antibodies after brucellin indicates previous or current infection. The results also show that repeated intracutaneous injections of brucellin will not sensitize normal persons to subsequent injections of antigen. Where doubt exists in the interpretation of any single skin-reaction, it seems that repetition of the test after a short interval will give valid results. We have encountered similar results in our investigation of clinical cases of suspected brucellosis, in which it has been our experience that in patients with active disease there is usually, but not always, a sharp rise in antibody titre after intradermal injection of brucellin. The increase in titre is sometimes tenfold, and we regard such an elevation of antibody content as confirmatory evidence in the diagnosis of active brucellosis, although failure to demonstrate an increased titre does not rule out the possibility of the disease (see Table, Cases 13 and 16). Since the completion of this investigation we have become familiar with the recent work of Krakauer, Rachman, and Neter (1951) and Carpenter, Deboer, Klein, and Tempereau (1950). Krakauer and his colleagues found that the agglutinin content of serum was increased after positive skin tests but unaffected by negative skin tests. Of 34 patients probably suffering from brucellosis and reacting to brucellergen, 32 showed a significant rise in antibody titre between the eighth and 22nd days after intradermal injection. Eighty-five control subjects failed to react to the skin test, and all 'failed subsequently to show significant agglutinin titres'. Similar results were obtained by Carpenter, Deboer, Klein, and Tempereau, who reported that brucella agglutinins appeared in 30 per cent. of 57 patients after a positive skin-reaction to brucellergen or brucella vaccine, but did not develop in any patient whose skin-reaction was negative.

Serum-agglutinins. It cannot be too strongly emphasized that serum-agglutinins will not be found in many cases of chronic brucellosis. It is by no means uncommon to isolate the organism from blood or marrow culture when no serum-agglutinins can be detected (Carpenter and Boak, 1930; Gilbert and Coleman, 1934; Huddleson, Scales, and Sorenson, 1936; Taylor, Lisbonne, Vidal, and Hazemann, 1938; Huddleson, Hardy, Debano, and Giltner, 1939c; Harris, 1948; Bower and Chudnoff, 1948; Scarlett, 1948). In view of the inconstant nature of saline agglutinins it was decided, at the outset of the present investigations, to search for the presence of incomplete agglutinins in the disease, especially in cases of chronic brucellosis, in which saline agglutinins

are often not demonstrable. It was decided to adapt the principles of the Coombs reaction, as used in the detection of Rh incomplete agglutinins, to the isolation of incomplete brucella antibodies. Morgan and Schütze (1946) had previously used a Coombs reagent in the identification of incomplete antibodies to *S. typhosum* and *Sh. shigae*, and a similar technique was adopted. Griffits (1947) had investigated the blocking properties of sera containing brucella antibodies, and had found that such sera prevented the agglutination of brucella organisms in a saline medium, but he found that freshly drawn normal sera also had this property. While our work was in progress, Jones and Wilson (1951) and Wilson and Merrifield (1951) published the results of their work on the incomplete antibodies of *Br. abortus* as demonstrated by the use of Coombs reagent. These authors were able to demonstrate high titres of incomplete agglutinins in the absence of saline agglutinins. Our own experience of these techniques has not been encouraging. We have confirmed the fact that incomplete agglutinins of high titre are often found when saline titres are low, but we have been unable to demonstrate significant titres of incomplete antibody in serum-negative cases of chronic brucellosis confirmed by liver biopsy. Using the technique of Wilson and Merrifield, we have investigated over 150 sera referred to us for *Br. abortus* antibody content. At the same time these sera have been tested in the usual way for saline agglutinins. In all cases in which saline agglutinins were present we were able to demonstrate incomplete agglutinins. The latter were usually, but not always, present in a much higher titre, the increase in antibody content being often tenfold. In no case, however, in which saline agglutinins were absent were we able to demonstrate incomplete agglutinins in titres over 1/80. In the present series of cases, therefore, the incomplete-agglutinin technique was of no assistance in the diagnosis of brucellosis, as high incomplete titres were invariably associated with significant titres of saline agglutinins. Our experience of this form of investigation, while admittedly limited, does not suggest that it will be of great value in the detection of chronic brucella infection.

Criteria for the diagnosis of chronic brucellosis. Apart from the isolation of the infecting organism there is no single criterion upon which the diagnosis of chronic brucellosis can be established and, as *Br. abortus* is notoriously difficult to isolate, the diagnosis is usually established by other means. We have elaborated a routine method of investigation which we believe will detect the majority of cases. In our experience the clinical history and examination of the patient are of the greatest importance in arriving at a diagnosis of chronic brucellosis. Much of the failure to detect such cases can be attributed to undue faith in bacteriological investigations. A long-standing history of night sweats and diffuse or localized muscle pain, in a patient who has not lost weight and does not look ill, should always suggest the diagnosis. If his occupation leads him into direct contact with cattle, the diagnosis is highly probable. We suggest that any patient who presents an ill-defined syndrome, and who has direct access to cattle, should be investigated for the presence of brucellosis. From the clinical examination enlargement of either the liver or the spleen will

usually be found. Lymphadenopathy is uncommon, but may occasionally be present. The erythrocyte sedimentation rate and blood count are usually within normal limits. In patients who present a suggestive clinical history, it is our routine practice to withdraw blood for agglutinin content and culture at the first attendance. At the same time an intradermal brucellin test is performed. The patient is next seen 48 hours later, when estimations of the saline serum-agglutinins and the skin-reaction are to hand. We accept a negative skin test and absence of serum-agglutinins as indicating the absence of infection. We have not yet encountered any patient with demonstrable agglutinins and a negative skin-reaction. The reverse finding, however, is not uncommon. In these latter patients search is again made two weeks later for serum-agglutinins, and a sharp rise in titre occurring during this interval is regarded as confirmatory evidence of active infection, always providing that the clinical history and examination strongly support the diagnosis. Patients in whom only a slight rise in titre has followed a positive intracutaneous test should be submitted to liver biopsy, by which the diagnosis is usually established.

The question is often asked 'What is a significant diagnostic titre of serum-agglutinins?' Some authorities regard a titre of 1/80 as significant, and others a titre of 1/320. There is an obvious danger in attempting to fix any arbitrary level of antibody titre as significant or diagnostic, since marked variations occur between different laboratories using the same serum for analysis; for example, Griggs and Case (1948) reported remarkable differences in the estimated brucella antibody titre, in the same sample of serum, reported by several different American laboratories of good repute. We prefer to answer this question in another way. We regard any titre of serum-agglutinins as significant, but no titre, however high, as in itself diagnostic of the disease. There is no doubt that in patients with a very high titre the chances of recovering the organism are greater than in those with a low titre; for example, Magoffin, Kabler, Spink, and Fleming (1949) found that over 90 per cent. of patients who yielded positive blood cultures had simultaneous agglutinin titres of 1/320 or higher. On the other hand, as we have pointed out, the number of patients with no demonstrable serum-agglutinins from whom the organism can be isolated is considerable, although the circumstances in this country differ from those in the United States, where infections with *Br. melitensis* and *Br. suis* are common. It is of interest from the standpoint of comparative pathology that Huddleson found that milk with an agglutinin titre of 1/25 is likely to be as heavily infected as milk with an agglutinin titre of 1/500 (Huddleson, Hardy, Debono, and Giltner, 1939b). According to Spink (1952) 'the higher the titre of agglutinins the more likely it is that one is dealing with an active case of brucellosis, and positive blood cultures are much more commonly associated with blood having a high titre of agglutinins'. We would point out, however, that recovery of the organism from the blood of sufferers from acute brucellosis is easier than in chronic cases, just as recovery of tubercle bacilli from the blood is more commonly successful in the acute and progressive forms of the disease; it would thus be fallacious to base the overall incidence of infection on the

results of blood culture. We finally emphasize the fact that the diagnosis of chronic brucellosis is in the hands of the physician, and that, until some simple and reliable ancillary investigation is elaborated, the results of the clinical examination of the patient should not be obscured by placing too much faith in bacteriological investigations.

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Summary

1. Attention is drawn to the lack of knowledge concerning the incidence of human brucella infection in Britain.
2. The clinical syndrome of chronic brucellosis is described with reference to 25 personally studied cases.
3. Twelve patients were subjected to aspiration liver biopsy. The characteristic nodular granulomata are described, and their appearances are compared with the lesions of 'other forms of sarcoidosis'.
4. An evaluation is made of other methods of diagnosis, with special reference to the brucellin skin test and serum agglutination reactions. The results are given of a limited investigation into the effects of brucellin on serum-agglutinins.
5. A routine method is described for the investigation of suspected cases of chronic brucellosis.

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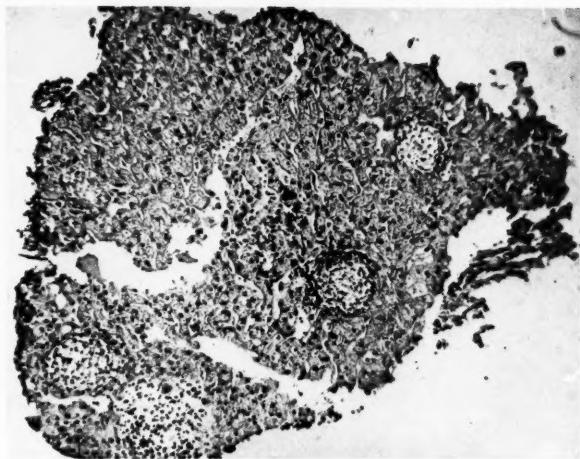


FIG. 1. Multiple brucella granulomata in liver (Case 1)
(haematoxylin and eosin, $\times 80$)

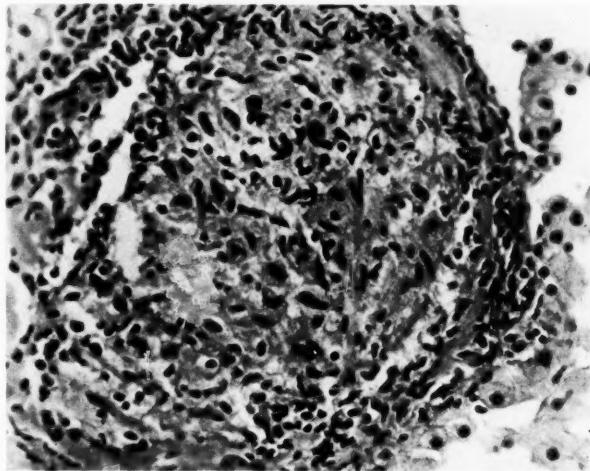


FIG. 2. High-power view of brucella granuloma in liver (Case 14)
(haematoxylin and eosin, $\times 360$)

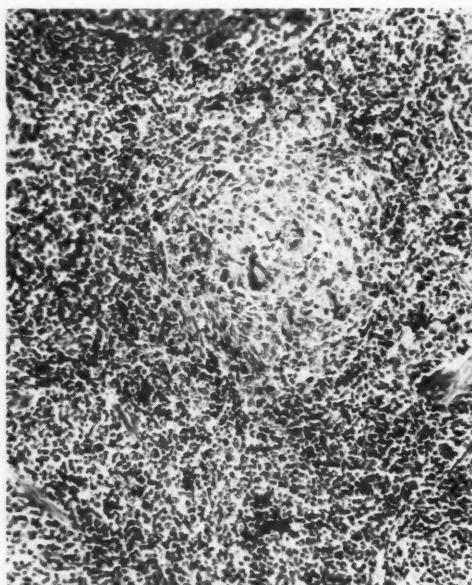


FIG. 3. Abortus granuloma in spleen of experimentally infected guinea pig (haematoxylin and eosin, $\times 130$)

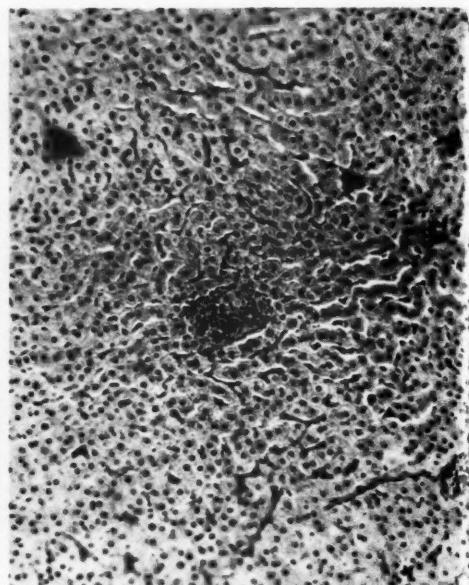


FIG. 4. Melitensis granuloma in liver of cow (haematoxylin and eosin, $\times 130$)

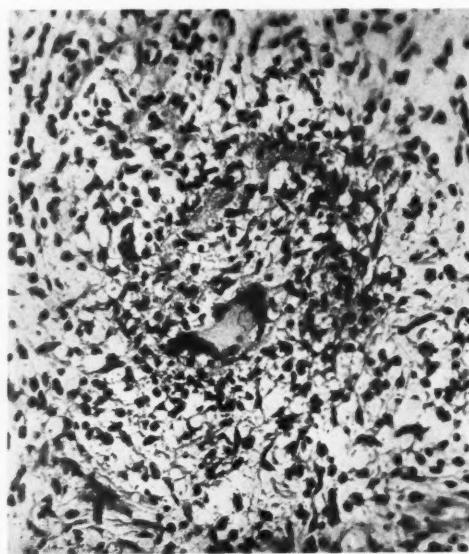


FIG. 5. Brucella giant-cell granuloma in skin of a veterinary surgeon (Case 22). (haematoxylin and eosin, $\times 290$)

THE HEART IN CHRONIC PULMONARY DISEASE¹

By R. M. FULTON

(From Crumpsall Hospital, Manchester, and the Department of Cardiology,
University of Manchester)

With Plates 5 to 8

THE fact that chronic pulmonary disease may result in heart failure has been recognized since the early nineteenth century (Laennec, 1819), but estimates of the frequency of this result have differed widely (Kountz, Alexander, and Prinzmetal, 1936; Griggs, Coggin, and Evans, 1939; Scott and Garvin, 1941; Spain and Handler, 1946). The object of the present investigation was to study the natural history and clinical features of chronic pulmonary disease associated with right ventricular hypertrophy. Congestive heart failure in patients with a chronic chest complaint may be due to unrelated heart disease, and Parkinson and Hoyle (1937) considered that heart disease caused by emphysema alone was surprisingly uncommon. The exclusion of past hypertension and ischaemic heart disease may be impossible during life, and it was therefore decided to confine the present investigation to cases in which necropsy was performed.

Methods

In 1950 and 1951 the diagnosis of pulmonary heart disease was made during life in 129 patients, all of whom were seen by the author, the majority being under close personal supervision. The diagnosis was based on clinical evidence which will be discussed later, and did not entail demonstrable right ventricular hypertrophy. Seventy-three patients died during the period of the investigation, and necropsy was performed on 58. The present account is confined to 50 of these cases in which our pathological criteria were fully satisfied. The pathological criteria used for the diagnosis of chronic pulmonary disease with cardiac involvement were:

1. Bilateral chronic pulmonary disease.
2. Absence of congenital, valvular, and ischaemic heart disease.
3. The presence of right and the absence of left ventricular hypertrophy.

The lungs were examined by the large-section technique of Gough, James, and Wentworth (1949). Ventricular hypertrophy has been estimated by most previous workers by measurement of the thickness of the ventricular walls (Griggs, Coggin, and Evans, 1939; Scott and Garvin, 1941; Spain and Handler, 1946), but this method is open to serious objections. The hearts in the present series were examined personally by the method described elsewhere (Fulton, Hutchinson, and Jones, 1952) which consisted of dividing the heart into two

¹ Received April 29, 1952.

parts, the free wall of the right ventricle and the left ventricle plus septum. The criterion for the presence of right ventricular hypertrophy was a right free wall weighing 80 gm. or more, and for the absence of left ventricular hypertrophy a left ventricle plus septum weighing less than 225 gm. In the absence of left ventricular hypertrophy, the ratio of the left ventricle plus septum to the right free wall (normally from 2·3:1 to 3·3:1) is a better index of the degree of right ventricular hypertrophy than the actual weight of the right free wall, for it takes into consideration the weight of the heart as a whole. Hearts were divided into three groups showing respectively slight (ratio from 1·84:1 to 1·4:1), moderate (ratio from 1·4:1 to 1·25:1), and gross (ratio from 1·25:1 to 1:1) right ventricular hypertrophy. Of the 58 cases which came to necropsy eight failed to satisfy the pathological criteria. Mitral stenosis was found in one case. In three left ventricular hypertrophy was present, and in four others the right ventricular weight was less than 80 gm. The remaining 50 cases, in which all the criteria were satisfied, form the material for the present study. Two cases in which the free wall of the right ventricle weighed 78·5 and 79 gm. are included, for the heart as a whole was small in both cases, and right ventricular hypertrophy was obvious on inspection.

Results

Aetiology

There were 46 male and four female patients, a preponderance of males also noted in the previous series of Parkinson and Hoyle (1937), Scott and Garvin (1941), and Spain and Handler (1946). Emphysema, with varying degrees of chronic bronchitis, was found in 42 cases, bronchiectasis in seven, and active bilateral pulmonary tuberculosis in one. Of the 42 patients with emphysema, one had facio-scapulo-humeral muscular dystrophy and a small unsuspected bronchial carcinoma, two had pronounced kypho-scoliosis, and another inactive pulmonary tuberculosis. Coincident emphysema was present in all seven cases of bronchiectasis. Four of the patients with chronic bronchitis and emphysema suffered, in addition, from recurrent attacks of true spasmodic asthma. In three of these cases asthma was the initial respiratory complaint, but in the fourth asthmatic attacks only developed after 16 years of chronic bronchitis. Accurate family histories were impossible to obtain, but there was nothing to suggest that heredity was of importance. Unlike the series of Thomas (1951), no specific industrial hazard was encountered. The commonest occupation was unskilled labouring, but a large variety of trades, indoor and outdoor, manual and sedentary, were represented. One factor common to all was exposure to the North Manchester atmosphere. The humidity is high, pollution with smoke and chemical fumes widespread and heavy, and fog common. Ten patients attributed their chest trouble to a definite severe respiratory infection, two to spinal disease at an early age with resulting chest deformity, and eight to gassing during the 1914–18 war. In the remaining 30 cases the onset was insidious. The approximate age at which chest disease started is shown in Table I.

Course of the disease-process

Once chronic chest disease was established, its progress could be divided into three stages.

1. *Stage of good exercise-tolerance.* For about 15 to 20 years patients complained of cough and sputum only.

2. *Stage of limitation of activity.* This stage was characterized by breathlessness on exertion, which in most cases was of insidious onset, but in a few started

TABLE I

Age at Onset of Chest Disease and Age at Death in 50 Patients

	Age (years)						
	0-9	10-19	20-29	30-39	40-49	50-59	60-69
Onset of chest disease in each decade . . .	6	5	17	18	4
Number of deaths in each decade	3	11	23	13

abruptly after a severe chest infection. The main feature of the dyspnoea was its variability. It was always worse in winter and especially in foggy weather, but there was a striking alteration in the exercise-tolerance from day to day. The patient's capacity for effort steadily diminished, and he was forced to stay off work for increasing periods each winter. In patients seen at this stage abnormal physical signs were confined to the respiratory system, and as the signs did not change with further progression of the disease it is convenient to describe the chest findings at this point. The antero-posterior diameter of the chest was increased, with slight to moderate non-angular kyphosis, but the 'barrel-shaped' chest was seen in four cases only. The chest expansion never exceeded one and a half inches. Cardiac dullness was decreased or absent, and the apex beat could be localized in only nine cases. Clubbing of the fingers was noticed in nine patients, five of whom had bronchiectasis and one chronic pulmonary tuberculosis, and was thus uncommon in cases of uncomplicated emphysema. The findings on percussion and auscultation varied with the underlying lesion, but in the patients with emphysema and bronchitis the presence of scattered rhonchi was the only abnormal physical sign, and the lung fields were clear on radiography. The duration of this stage was from two to five years.

3. *The terminal stage.* This was a stage of almost total disability, lasting from a few months to two years. In addition to cough, sputum, and dyspnoea on exertion, loss of weight was a common complaint; with few exceptions the patients were thin, and they were often cachectic (Table II). During this stage peripheral oedema was first noticed. The average age at death was 53 years (Table I). Three fairly distinct clinical pictures, each with its own problems, were seen in the terminal stage.

A. *Congestive heart failure.* In 20 fatal cases congestive heart failure was the main feature. Cyanosis was always present, but varied in intensity even in the same patient, and was often slight. It was combined with a rather shallow

'muddy' complexion, described by Laennec (1819) as 'earthy'. Sinus tachycardia was the basic rhythm in all cases. Ectopic rhythms occurred in three cases (auricular fibrillation in two, and 2:1 auricular tachycardia in one), but never lasted longer than 48 hours. The blood-pressure was always within normal limits, the systolic pressure tending to be low. An inspiratory fall in the systolic pressure of as much as 20 mm. Hg was noted in many cases, but similar readings were obtained in patients with emphysema and asthma who

TABLE II
Body-Weight in 27 Patients

	<i>Body-weight (lb.)</i>				
	84-97	98-111	112-25	126-39	over 140
Patients without oedema	6	7	3	..	3
Patients with oedema	1	4	1	2
Total	6	8	7	1	5

had no cardiac involvement, and it is doubtful if this sign is as helpful as Kennedy (1943) suggested. Enlargement of the heart was demonstrable clinically in two cases only, and auscultation was rendered difficult by overlying emphysematous lung and respiratory adventitia. The second sound in the pulmonary area was seldom heard with clarity, and was accentuated in one case only. Other writers (Coggin, Griggs, and Stilson, 1938; Willius, 1946; Kennedy, 1943) have regarded this sign as of value, and it may be that the increased incidence and severity of chronic bronchitis in the present series accounts for this difference of opinion. Gallop rhythm, which developed under observation in four cases, was heard at the left sternal border in 10 patients, only one of whom survived longer than four months after the gallop appeared. A systolic murmur, varying in quality from soft to blowing, was present over the lower sternum in six patients. It was associated with distension of the neck veins to the angle of the jaw or beyond, and with very considerable right ventricular hypertrophy and dilatation at necropsy, and may have been due to relative tricuspid incompetence. Congestive failure, with moderate to gross peripheral oedema, was always present. Oedema of the upper limbs occurred in six cases, and was probably due to the fact that patients often found breathing easier when they sat forwards in bed leaning on their hands, a position comparable to 'squatting' in cyanotic congenital heart disease. Hydrothorax was seen on one occasion only, in a patient with massive oedema extending above the costal margin. Radiology revealed right ventricular enlargement, with slight to moderate increase in the transverse diameter of the heart. Serial films showed that cardiac enlargement was a late development in the disease-process (Plate 5, Fig. 4). The electrocardiographic findings will be discussed in detail in another paper. Praecordial leads showed definite evidence of right ventricular hypertrophy (criteria of Myers, Klein, and Stofer, 1948) in 14 of the 20 patients, and complete right bundle-branch block in two. At necropsy right ventricular hypertrophy was gross in 11, moderate in six, and slight in three

cases. The lungs were bulky, with a few bullae at the margins. Emphysema was widespread microscopically, but was not conspicuous on naked-eye examination (Plate 6, Fig. 5).

The commonest diagnostic error in patients with chronic bronchitis and emphysema with heart failure is to overlook associated heart disease due to other causes. The murmur of a valvular lesion may be obscured, and ischaemic heart disease may be difficult to exclude. The following findings suggest a complicating factor. 1. *Cardiac pain.* Pleuritic pain, and tightness in the chest produced by coughing or severe dyspnoea, occurred in uncomplicated cases, but were easily distinguishable from the pain of coronary disease. 'Hypercyanotic angina' has been described (Viar and Harrison, 1952), but it is doubtful whether angina occurs as a result of oxygen unsaturation in the absence of coronary disease. 2. *Paroxysmal nocturnal dyspnoea.* Breathlessness at night, usually on first lying down, might follow a bout of coughing or be due to an attack of bronchial asthma. Cardiac asthma did not occur. 3. *Sudden increase in dyspnoea.* Except when an acute respiratory infection produced sudden deterioration, the progress of the disease was slow and gradual. 4. *Clinical cardiac enlargement.* 5. *Sustained auricular fibrillation.* 6. *Abnormal left axis deviation, or left bundle-branch block.* These electrocardiographic findings were never seen in an uncomplicated case. 7. *Age over 65 years.* Only two proved cases were seen in patients over the age of 65 years. Degenerative heart disease is a more probable cause of symptoms in old people. 8. *Obesity.*

The investigation was not designed for a critical evaluation of treatment, and therapeutic agents were generally used in combination. The response to a particular line of treatment varied from patient to patient, and even in the same patient at different times. Digitalis, although not apparently harmful, was of little value, and results such as those described by Ferrer, Harvey, Cathcart, Webster, Richards, and Cournand (1950) were not obtained. Mersalyl injections reduced oedema in most cases, but clinical improvement did not always parallel reduction of oedema. Antibiotics nearly always improved dyspnoea, and sometimes reduced oedema when digitalis and mersalyl had failed (Fig. 1). A combination of penicillin and mercurial diuretics appeared to be the most satisfactory form of therapy. Oxygen was of doubtful benefit. Patients said they obtained relief from intermittent oxygen by B.L.B. mask, but tended to become addicted to it. Our experience is in agreement with the observation of Whitfield, Arnott, and Waterhouse (1950) that antispasmodics are of value only in the presence of asthma. Table III shows the survival period after the onset of oedema. Nine patients died in the first episode of failure, nine in the second, and two in the third. None survived longer than 18 months.

B. *Acute broncho-pulmonary infection.* In 16 cases the immediate cause of death was an acute respiratory infection. There had been a recent increase in cough and dyspnoea, the sputum being more copious and purulent than usual. Slight oedema was present in every case, but five patients had never noticed any swelling, and in eight others the oedema had been present for less than three weeks before admission. The patient was always much more ill than the degree

of congestive failure would suggest. He was orthopnoeic, moderately to deeply cyanotic, and not infrequently delirious. The complicating acute infection was acute bronchitis or bronchopneumonia in 13 cases and lobar pneumonia in three. A short paroxysm of auricular fibrillation occurred in one patient, gallop rhythm in four, and a systolic murmur over the lower sternum in three. An electrocardiogram was available in nine cases, only three of which showed

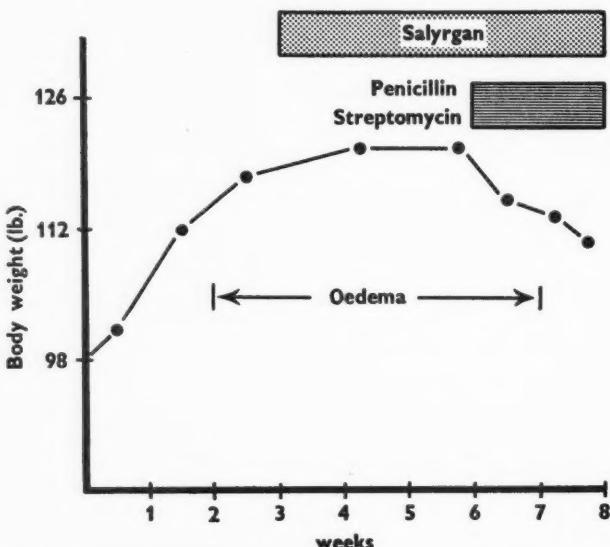


FIG. 1. Chronic pulmonary disease with congestive heart failure.
The effect of antibiotics in reducing oedema.

definite right ventricular hypertrophy. Cardiac enlargement was detected clinically in one case only. Nine patients died within 48 hours of admission to hospital. At necropsy right ventricular hypertrophy was gross in three,

TABLE III
Survival of Patients after Appearance of Oedema
Survival period (months) after appearance of oedema

<i>Cause of death</i>	<i>Survival period (months) after appearance of oedema</i>					
	<i>Less than 1</i>	<i>1-3</i>	<i>3-6</i>	<i>6-12</i>	<i>12-18</i>	<i>Over 18</i>
Congestive heart failure . . .	1	5	6	5	3	..
Acute respiratory infection . . .	11	4	..	1†
Anoxia . . .	3	6	1‡	..
Other causes . . .	2*	1	1
Total . . .	17	16	6	6	4	1

* Includes one case in which failure was never present.

† This patient recovered from a first episode of failure due to respiratory infection.

‡ This patient recovered from a first episode of failure due to transient auricular fibrillation (Case 35; see Appendix).

moderate in eight, and slight in five cases. The lungs showed evidence of acute infection in addition to chronic lung disease.

The importance of this common clinical picture cannot be over-emphasized, since it is often unrecognized, and there is a reasonable chance of recovery if the condition is treated promptly. The infective basis of the failure may not be appreciated, and in several cases the terminal infection was recognized only

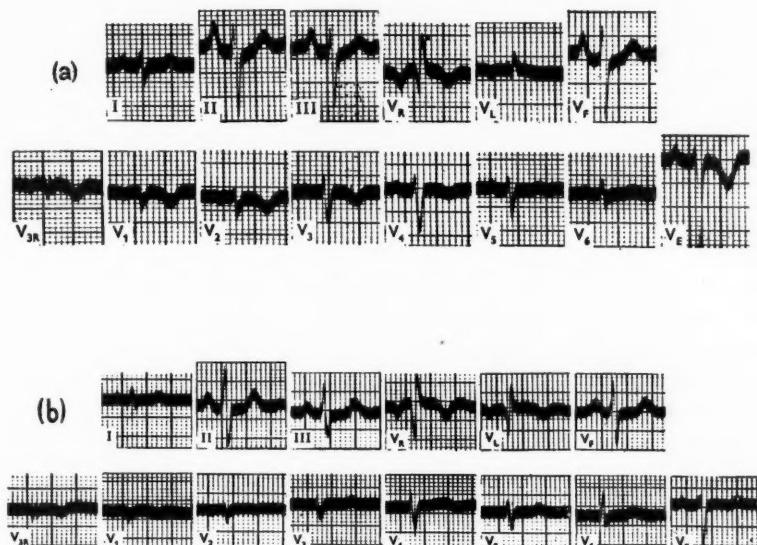


FIG. 2. Chronic pulmonary disease with acute infection. Electrocardiograms (a) on February 12, 1951, showing T-wave negativity in the right praecordial leads during an acute respiratory infection, and (b) on April 16, 1951, after recovery.

at necropsy. The following features tend to focus attention on the heart; to illustrate some of the points, reference is made to patients who recovered from such an episode, and who do not therefore strictly belong to the present series.

1. *The occult nature of the infection.* Nine of the 16 patients had no pyrexia, although in every case in which it was estimated the white-cell count was over 15,000 per c.mm. In patients with acute bronchitis or bronchopneumonia the physical signs were not striking, and differed little from those found in a quiescent phase.
2. *The presence of congestive failure and gallop rhythm.*
3. *Temporary hypertension:* nine survivors showed a rise in blood-pressure lasting for two or three days during the acute stage. In five of these patients the systolic pressure only was raised (up to 185 mm. Hg). In four both systolic and diastolic pressures were increased, for example, to 180/120 and 210/110. In every case the pressure returned to normal after recovery. The pressure was known to have been normal before the episode in two patients, and in two others, who subsequently died, necropsy revealed no left ventricular hypertrophy, no coronary

disease, and no renal evidence such as arteriolosclerosis to suggest that sustained hypertension had been present during life. This temporary hypertension may have been due to the muscular effort of fighting for breath. 4. *Electrocardiographic changes.* Five survivors had sharp T-wave inversion in right praecordial leads, which, combined with tiny R waves due to clockwise rotation, gave a

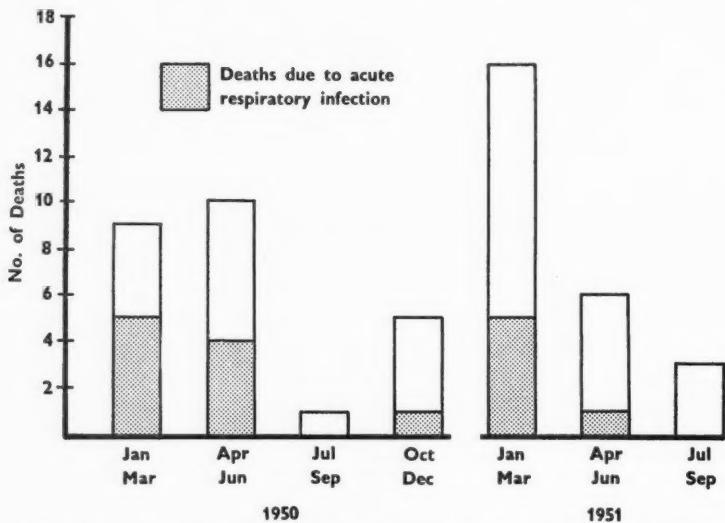


FIG. 3. Seasonal incidence of deaths in the series showing the reduction in the proportion of patients who died of acute respiratory infection in 1951 as a result of early antibiotic therapy.

picture not unlike that of antero-septal infarction. The T-wave inversion diminished or disappeared with recovery (Fig. 2), and in three fatal cases necropsy revealed no evidence of myocardial infarction.

A mistaken diagnosis of hypertensive failure or cardiac infarction may be disastrous, for treatment directed solely towards the heart failure is without effect, and morphine may be lethal. There is little time for second thoughts, for death often comes rapidly and unexpectedly. The treatment is an immediate course of antibiotics. Results were often dramatic: the patient's general condition improved rapidly, and the oedema disappeared in a few days without other therapy. Oxygen was of value in the acute stage. To prevent the therapeutic failures which had resulted from mistaken diagnosis in earlier cases, all patients in whom acute infection was suspected were given an immediate course of penicillin (1 million units daily). Some patients proved resistant to penicillin, and streptomycin (0.5 gm. six-hourly) was also given immediately to patients who were very ill. The result of this routine was a decrease in the incidence of acute infection as a cause of death in chronic pulmonary disease, in spite of the influenza epidemic of early 1951 (Fig. 3). When congestive failure was precipitated by an acute respiratory infection the mortality was about 25 per

cent., even with immediate antibiotic therapy. It might have been less if treatment had been started earlier, for many patients were admitted in a moribund condition. Both patient and practitioner tend to underestimate the importance of acute respiratory episodes in view of their frequency in the past, and it is not easy to get such patients admitted to hospital. The ultimate outlook is poor, all patients so far observed having died within two years of the onset of oedema, even when the failure had been precipitated in the first instance by an acute infection.

C. Anoxia. Ten patients died without acute respiratory infection and with minimal congestive failure. All had been severely restricted in activity for many months, many being unable to walk more than 100 yards. Although oedema was detected in every case on admission, it was always slight, and six patients had never noticed swelling of the legs. Four were admitted because of severe dyspnoea, and two because of mental disorientation. All showed cyanosis, and four, including the two who had mental symptoms, were plum-coloured. All these patients had sinus rhythm with or without tachycardia, but transient auricular fibrillation was noted in two cases. Gallop rhythm was heard in four cases, and a systolic murmur at the left sternal border in one case. White-cell counts were made in nine cases, and never exceeded 12,000 per c.mm. Radiologically the transverse diameter of the heart was within normal limits, or but slightly increased; the pulmonary conus was more prominent than usual, and the hilar shadowing increased: the peripheral lung fields were clear (Plate 7, Fig. 6). In no case did the electrocardiogram show definite evidence of right ventricular hypertrophy. With rest in bed oedema decreased or disappeared in all but two patients, one of whom had previously been thought to have Addison's disease because of a low systolic blood-pressure and general weakness. Treatment with deoxycorticosterone acetate, rather than heart failure, was the probable cause of a rapid terminal increase of oedema in this case. In spite of the reduction of oedema the general condition deteriorated in every case. The patient became drowsy and apathetic, or disorientated and irrational, often with delusions of persecution. Cyanosis persisted, but towards the end dyspnoea often disappeared and patients were able to lie flat in bed. Muscular twitching of the limbs was noticed. This state, which lasted up to a month, invariably culminated in death. Apart from the cyanosis there was a strong clinical resemblance to uraemia, but in the seven cases in which the blood-urea was estimated terminally it never exceeded 50 mg. per 100 ml. At necropsy right ventricular hypertrophy was gross in one case, moderate in three, and slight in six. The lungs were bulky, bullae numerous and often large, and large emphysematous spaces could be seen with the naked eye in whole-lung sections (Plate 8, Fig. 7).

In the absence of grossly abnormal physical signs there was a reluctance in this type of case to attribute the severe symptoms to emphysema and chronic bronchitis. Too much importance was attached to the negative X-ray and electrocardiogram, and too little to the clinical history, the patient being regarded as neurotic or a malingerer, often until shortly before death. The

difficulties are illustrated in the Appendix. Antibiotics were tried in seven cases, mercurial diuretics in four, and digitalis in three, without benefit. Oxygen by B.L.B. mask was poorly tolerated, and produced no improvement. Once this stage was reached the outcome was invariably fatal. A similar clinical picture was seen in a few patients during an episode of acute respiratory infection, in whom recovery followed antibiotic treatment.

D. *Other causes of death.* 1. *Peptic ulceration.* Two patients, admitted with congestive failure and already in the terminal stage of the disease-process, died from sudden gastro-duodenal haemorrhage. Evidence of peptic ulceration was found at necropsy in nine patients (18 per cent.). Except in one case the ulceration was recent, and except in the two patients who had haemorrhage it was unsuspected during life. Browne and Vineberg (1932) suggested that hyperchlorhydria might be a result of high arterial carbon-dioxide levels, and this mechanism may operate in chronic pulmonary disease. The results of fractional gastric analysis are not available in the present series. 2. *Pulmonary embolism.* One patient had a deep venous thrombosis after recovery from congestive failure, and died from pulmonary embolism. 3. ? *Ruptured bulla.* One patient, bedridden in hospital for months with extreme dyspnoea, although without heart failure, died suddenly. Death was thought to have been due to rupture of one of the numerous large bullae found at necropsy. Right ventricular hypertrophy was slight.

Discussion

Previous workers (Brooks, 1948; Thomas, 1951) found difficulty in correlating the pulmonary with the cardiac pathology in chronic pulmonary disease, and noted that some patients die, apparently without other disease, and yet with little right ventricular enlargement and without heart failure. In the 50 patients of the present series, all of whom died as a direct result of chronic lung disease, two distinct modes of termination were observed. In one group pronounced right ventricular hypertrophy developed, and death was due to congestive heart failure. In the other group, in which right ventricular hypertrophy was slight and congestive failure slight or absent, death was apparently due to cerebral anoxia. The two groups can be called congestive and anoxic respectively, terms descriptive of the presenting clinical features in the terminal stage of the disease-process. Of the cases which were terminated prematurely by acute infection or other causes, five had already shown signs of considerable right ventricular hypertrophy and congestive failure, and three had shown signs of severe anoxaemia without cardiac involvement, so that altogether 25 cases could be classed as congestive and 13 as anoxic. In the remaining 12 cases there was insufficient evidence to assign them to one or the other group. Table IV summarizes the main distinctive features of the two groups. It has been shown (McMichael, 1948; Harvey, Ferrer, Richards, and Cournand, 1951) that right ventricular hypertrophy in chronic pulmonary disease is due to pulmonary hypertension. Although the cause of the pulmonary hypertension has not been conclusively demonstrated, it is probable that several factors operate, of which

a reduction in the pulmonary capillary bed and anoxaemia are important (Harvey, Ferrer, Richards, and Cournand, 1951). It was technically impossible in the present study to measure the pulmonary arterial pressure or the arterial oxygen saturation, but indirect evidence (radiological increase in the hilar shadowing, and the presence of pulmonary atheroma at necropsy) suggested that pulmonary hypertension was present in the anoxic as well as the congestive

TABLE IV
Main Contrasting Features of Congestive and Anoxic Cases

Type of case	Number of cases	Right ventricular hypertrophy			Chest disease: duration less than 15 years	Severe infective episodes		
		Degree at necropsy						
		Slight	Moderate	Gross				
Congestive	25	3	8	14 (56%)	18 (72%)	2 (8%)		
Anoxic	13	8	4	1 (8%)	0	6 (46%)		
						14 (56%)		
						2 (15%)		

group. Actually the destruction of the pulmonary capillary bed was greater, and the cyanosis more pronounced, in the anoxic than in the congestive group, although, as Selzer (1951) points out, cyanosis cannot be used as a measure of arterial oxygen unsaturation. Nevertheless, the right ventricular hypertrophy was much less. It is doubtful whether there is a fundamental difference in the nature of the lung disease in the two types of case, for clinically they were indistinguishable until shortly before death, and in those cases which were terminated early by acute infection there were not the gross pathological differences which may be apparent later. The paradox may be explained by a difference in the tempo of the disease-process in the two groups. In six of the anoxic group (46 per cent.) the duration of the chest disease was less than 15 years, compared with only two of the congestive group (8 per cent.). Right ventricular hypertrophy is a late development in chronic pulmonary disease, the heart apparently being able to tolerate a raised pulmonary pressure for many years. It may be that, in the anoxic group, the progress of the lung disease is relatively so rapid that death takes place as a result of lung destruction before pulmonary hypertension has been present long enough to cause much right ventricular hypertrophy. Another difference was in the incidence of severe acute respiratory infection. In the congestive group 14 patients (56 per cent.) gave a history of such episodes, compared with two (15 per cent.) in the anoxic group; no patient with bronchiectasis died an anoxic death. The significance of this difference is doubtful, but it has been shown (Harvey, Ferrer, Richards, and Cournand, 1951) that there is a sharp rise in pulmonary arterial pressure during acute infections.

In spite of the differences between the two groups, it must be repeated that they are clinically indistinguishable until within two years of death. The name 'chronic cor pulmonale', which has become popular in recent years and can be applied properly to the congestive group only, is an unfortunate one, for it has given rise to the dangerous belief that chronic pulmonary disease is only serious

when right ventricular hypertrophy can be detected. It is not sufficiently realized that patients can die from chronic pulmonary disease without heart failure. The present study shows that, of all patients dying as a result of chronic pulmonary disease, only about one-half die from congestive failure. One-quarter die from superadded acute respiratory infection, and the remaining quarter from the chronic pulmonary disease itself. A better concept of the disease-process, from the point of view both of diagnosis and of treatment, would be to think of it as 'pulmonary failure', a process in which heart failure may be a terminal incident.

Increasing knowledge of the altered haemodynamics and respiratory function in chronic pulmonary disease has not been reflected in earlier diagnosis or more effective treatment. The tendency is for diagnosis to be delayed until the appearance of congestive failure, or until the last few months of life in the anoxic cases, when even palliative treatment has little to offer. As a result of a better understanding of the natural history of the disease it became possible to diagnose the condition at the stage of dyspnoea on exertion. The diagnosis is made from the long history of chest trouble, with the characteristically variable dyspnoea. The most important physical sign is a reduction in the chest expansion to one and a half inches or less, but confirmatory evidence of pulmonary hypertension may be obtained radiographically from increased hilar shadowing. The presence of cardiac enlargement or definite electrocardiographic abnormality indicates that the condition has reached an advanced stage or is complicated by other cardiac disease. Although nothing can be done to alter the basic lung lesion, one can, by early and adequate treatment of acute respiratory infections, do something to slow down the progress of the disease. Acute bronchitis in a chronic bronchitic is not usually regarded as a serious matter, but each episode, by reducing further the amount of effective lung tissue, and possibly by raising the pulmonary arterial pressure, can do considerable harm. At any stage treatment of the lung disease is more likely to be of benefit than treatment of the heart.

It is difficult to assess the absolute incidence of uncomplicated chronic pulmonary diseases as a cause of death, but in Crumpsall Hospital it ranked in frequency with rheumatic, hypertensive, and ischaemic heart disease. There is, however, a notable difference between teaching and non-teaching hospitals in this respect. It is even more difficult to estimate the frequency with which pulmonary failure, with or without heart failure, terminates chronic pulmonary disease. In the present series chronic pulmonary disease was established before the age of 30 years in 56 per cent. of cases, and before the age of 40 years in 92 per cent. (Table I). As the average duration of the disease-process is from 25 to 30 years, it is to be expected that patients developing chronic chest disease in middle or later life (as in the series of Parkinson and Hoyle, 1937) will die from unrelated diseases. If chest disease is established before the age of 30 years it appears that death from pulmonary failure is likely. Chronic chest disease in industrial areas such as Manchester is an important cause of morbidity and mortality, and one which has received less than its due publicity. The average

age at death was 53 years, and nearly all the patients had been unfit for regular work for several years before death. Although earlier diagnosis and more energetic treatment of acute respiratory episodes may prolong life in individual cases, the problem as a whole can only be solved by preventive measures. There is no proof that atmospheric conditions actually initiate chest disease, but there is no doubt that the chemical-laden fog of Manchester was responsible for the majority of acute exacerbations. The effect of a foggy day could almost be used as a diagnostic test, for it invariably intensified the cyanosis and dyspnoea of chronic pulmonary disease, and left other cardiac patients undisturbed. Purification of the atmosphere is a public health measure long overdue, and one which would soon repay itself in a reduction of chronic respiratory disease.

'... Poor wretches, drinking in disease with every breath, with their own funeral pall hanging over them, in that canopy of fog and poisonous smoke, from their cradle to their grave.'—Charles Kingsley, *Alton Locke*.

My thanks are due to the Consultant Physicians at Crumpsall Hospital for permission to examine patients under their charge, and to members of the resident medical, nursing, and ancillary staffs, too numerous to mention, for their enthusiastic co-operation in the investigation. In particular I wish to acknowledge my indebtedness to Dr. J. Davson for his valuable help in the pathological aspects of the work, to Dr. A. Morgan Jones for his constant help and encouragement, and to Professor Crighton Bramwell for his criticism and advice in the preparation of this paper.

The paper is based on a thesis accepted for the degree of Doctor of Medicine of the University of Edinburgh.

APPENDIX

Case Reports

Case 14. Death from congestive heart failure. J. D., a general labourer aged 41 years, was admitted to hospital on February 2, 1950, with right upper lobar pneumonia. He had complained of cough and purulent sputum since 1930, but had remained able to work. He responded to treatment with penicillin, but radiography revealed residual fibrosis and pleural thickening. There was no cardiac enlargement, and the blood-pressure was 140/80. After this illness the patient complained of persistent and severe dyspnoea on exertion, and was readmitted to hospital on September 26, 1950, because of oedema of the legs of a fortnight's duration. On examination he was thin (weight 94 lb.), and his complexion was sallow, with slight cyanosis. Clubbing of the fingers was present. The heart rhythm was of sinus origin, and the blood-pressure, which was 180/120 on admission, settled to 110/70 after a few days. The heart sounds were of good quality, and there were no murmurs. Slight distension of the neck veins was present, and there was moderate oedema of the legs, thighs, and sacrum; the liver was enlarged. The chest expansion was reduced to one inch, and widespread rhonchi were heard over both lungs. Although not detectable clinically, considerable cardiac enlargement was shown radiographically, and the electrocardiogram showed right ventricular hypertrophy. With rest in bed, digitalis, and salyrgan the oedema subsided slowly, and he was allowed to go home on November 15, 1950; but when seen as an out-patient a month later he again

had slight oedema of the legs, and was unable to walk more than 15 yards. He was readmitted on December 19, 1950, with extensive oedema. Physical signs were unchanged except that gallop rhythm was heard for the first time. Treatment was without effect, and he died on January 1, 1951. At necropsy bilateral emphysema was present, with bronchiectatic cavities in the right upper lobe. The heart showed moderate right ventricular hypertrophy (right free wall 150 gm., left ventricle plus septum 193 gm., ratio L+S/R = 1.28:1).

Case 26. Death from acute broncho-pulmonary infection. H. R., a mill-manager aged 53 years, was admitted to hospital on March 5, 1950. He had complained of cough and sputum ever since whooping-cough in infancy. Since 1935 he had been off work most winters with acute bronchitis, and had been breathless on exertion for five years, severely so for one year. For a fortnight cough and dyspnoea had been much more troublesome, and two days before admission he had noticed swelling of the ankles for the first time in his life. On examination he was cyanotic and orthopnoeic. Sinus tachycardia at a rate of 100 per minute was present, and the blood-pressure was 130/100. The cardiac apex was not localized, and there were no murmurs, but gallop rhythm was audible. Slight neck-vein distension, slight oedema of the ankles, and hepatomegaly were present, and there were widespread rhonchi in both lungs. The electrocardiogram showed abnormal right axis deviation, but no definite evidence of right ventricular hypertrophy in the praecordial leads. Although there was no pyrexia, he was treated with penicillin and oxygen, but died within 48 hours. Necropsy showed bilateral emphysema, with peribronchial round-cell infiltration, congestion, and haemorrhage in both lower lobes. There was moderate right ventricular hypertrophy (right free wall 125 gm., left ventricle plus septum 176.5 gm., ratio L+S/R = 1.4:1).

Case 35. Death from anoxia. A. M., a lorry driver aged 43 years, was admitted to hospital on December 12, 1948, at his own request, his doctor having declined to recommend his admission. He had first complained of cough while serving in the Army in Iceland during the 1939-45 war, and was discharged in 1943 because of 'psychoneurosis'. In 1946 he began to notice that shortness of breath was becoming a handicap to him. He was examined by a consultant physician in 1947, and by another in 1948, both of whom regarded his symptoms as 'functional', but early in 1948 he had to give up work altogether. On examination he was thin (weight 106 lb.), cyanotic, and dyspnoeic, and auricular fibrillation was present with a ventricular rate of 120 per minute, the blood-pressure being 130/95. The apex beat was impalpable, and the heart sounds were of good quality. Slight neck-vein distension, slight oedema, and hepatomegaly were noticed, and scattered rhonchi were heard over both lungs. He was digitalized, and by next morning sinus rhythm had been restored, and the oedema subsided in a day or two. A radiograph of the chest showed no cardiac enlargement, but the main pulmonary artery was prominent and the hilar shadows were more dense than normal (Plate 7, Fig. 6). An electrocardiogram showed abnormal right axis deviation. There was no definite evidence of right ventricular hypertrophy, but the T waves were sharply inverted over the right praecordium. Ischaemic heart disease was suspected, and he was kept in bed for four weeks. On getting up he could not walk more than half the length of the ward without getting breathless. In the absence of grossly abnormal signs his dyspnoea was not taken seriously, and he was reassured and discharged. He was readmitted, again at his own request, on April 2, 1949, still complaining of severe dyspnoea. No further abnormalities were made out on examination; he had no congestive heart failure, and was discharged after three weeks with

scant sympathy. In September 1949 he was seen at another hospital, and was thought to be a malingerer. On January 12, 1950, he was admitted to hospital for the last time. His cyanosis was slightly deeper in shade. Sinus rhythm was still present, the blood-pressure was normal, and there was no cardiac enlargement. No oedema was detected, but the liver was slightly enlarged. For the first time his chest expansion was measured, and was found to be three-quarters of an inch. He was treated with theophylline ethylene-diamine and ephedrine, but his general condition deteriorated. He became weak, and later disorientated, and died on April 12, 1950, without ever having had more than slight oedema. At necropsy there was gross emphysema of both lungs, the left upper lobe consisting almost entirely of one large bulla. Atheroma of the main pulmonary arteries was present, and there was an active recent peptic ulcer on the lesser curvature of the stomach. Right ventricular hypertrophy was slight (right free wall 112 gm., left ventricle plus septum 159 gm., ratio L+S/R = 1.42:1).

Summary

On the basis of 50 cases with necropsy confirmation, the natural history of chronic pulmonary disease with right ventricular hypertrophy is described, and the diagnosis, prognosis, and treatment are discussed.

In the terminal stage two main groups of cases were recognized: (1) congestive, in which right ventricular hypertrophy was considerable and death was due to congestive heart failure, and (2) anoxic, with slight right ventricular hypertrophy, little congestive failure, and death from cerebral anoxia. Although right ventricular hypertrophy was less pronounced in the anoxic group, the amount of lung destruction was greater. It is suggested that this difference may be explained by a more rapid rate of progression of the lung disease in the anoxic group. A proportion of patients (24 per cent.) died from acute respiratory infection or other causes before differentiation into the congestive or anoxic pattern had taken place.

'Chronic cor pulmonale' is regarded as an unsatisfactory name, for only one-half of the patients with fatal uncomplicated chronic pulmonary disease died from congestive heart failure. The other half died from acute respiratory infection or from the chronic pulmonary disease itself, but were clinically indistinguishable from those with congestive failure until shortly before death. It is suggested that the term 'pulmonary failure' would better describe the disease-process.

Peptic ulceration was present in nine cases, and was the immediate cause of death in two.

Early diagnosis is important, and more energetic treatment of acute bronchopulmonary infections prolongs life. The value of antibiotic therapy at all stages is emphasized.

Chronic pulmonary disease is an important cause of morbidity and mortality in middle-aged men in an industrial area, and atmospheric pollution is considered to be an important aggravating factor.

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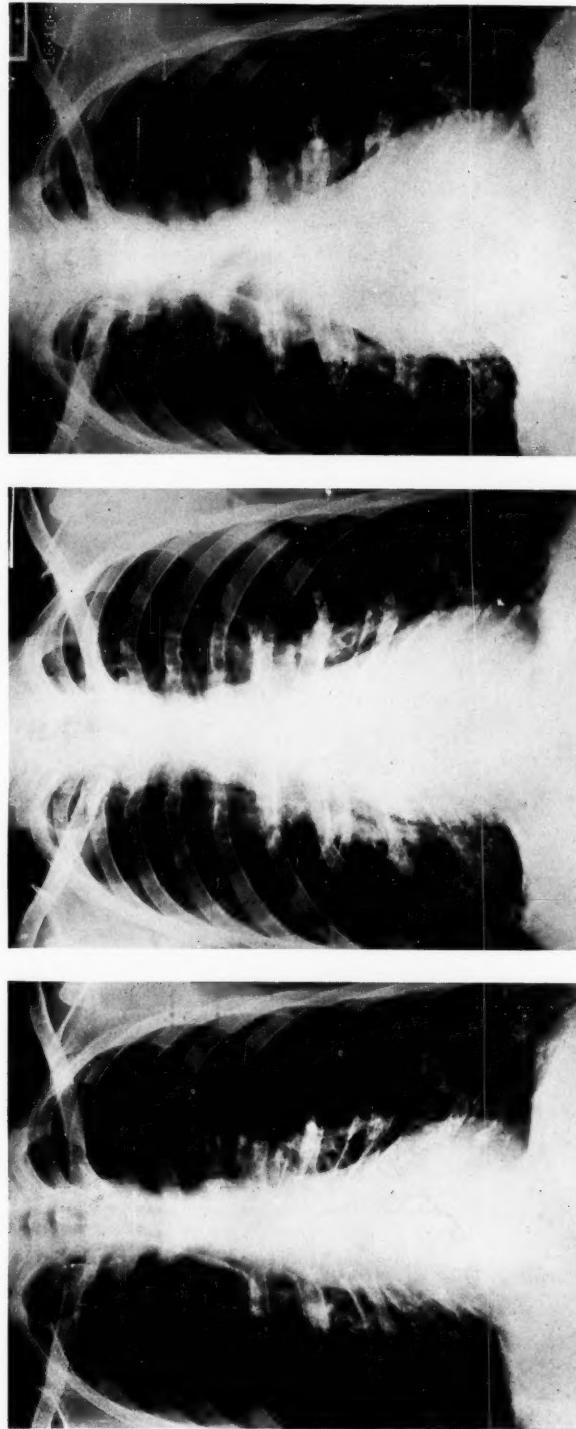


FIG. 4. Serial teleradiographs of a patient who died on January 9, 1951, of congestive failure, showing late development of cardiac enlargement

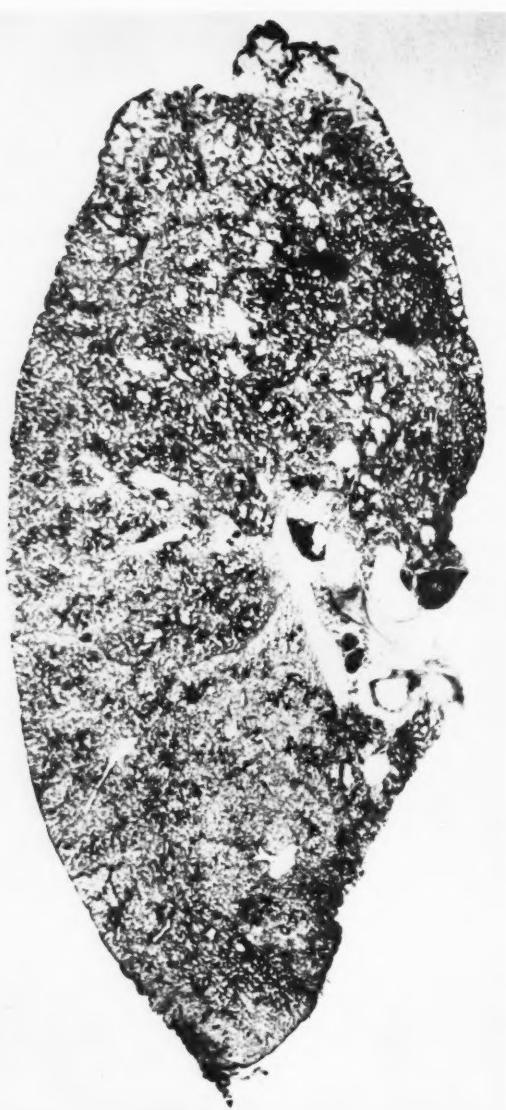


FIG. 5. Whole-lung section from a patient who died of congestive heart failure

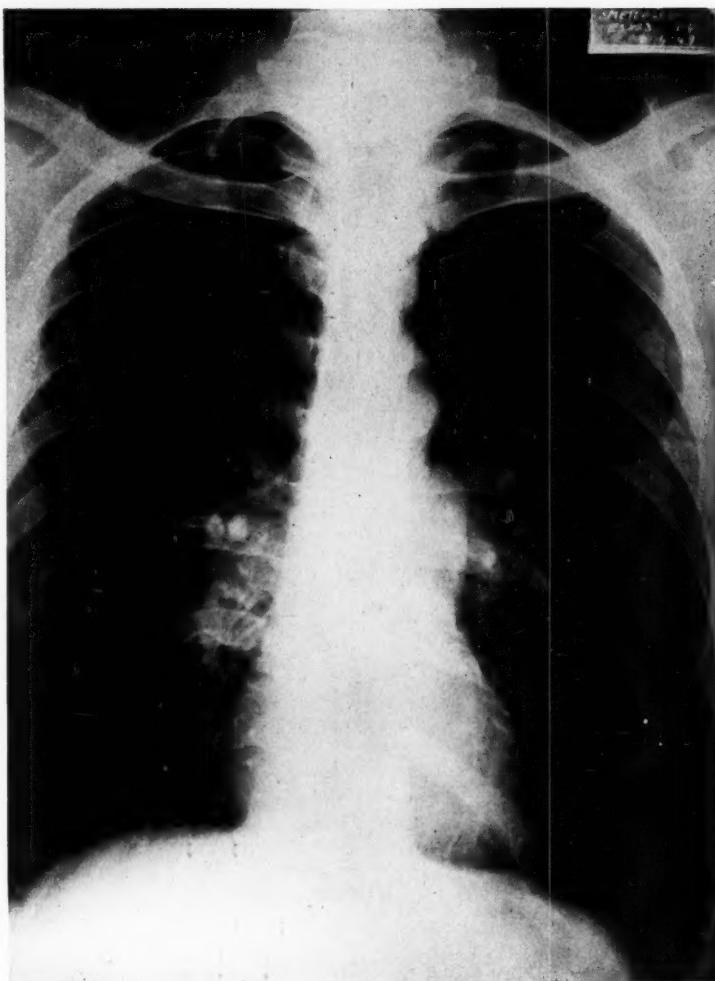
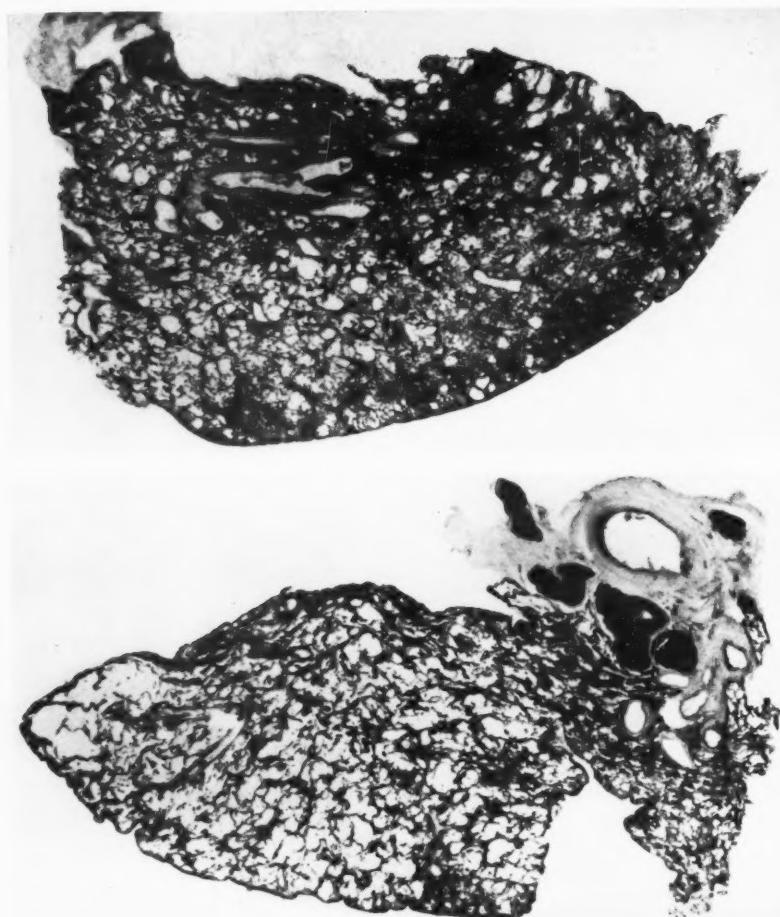


FIG. 6. Teleradiograph of an anoxic patient



Lower lobe

Upper lobe

FIG. 7. Whole-lung section from an anoxic patient

SYMPTOMS, SIGNS, AND DIAGNOSTIC FEATURES OF IDIOPATHIC STEATORRHoeA¹

By W. TREVOR COOKE, A. L. P. PEENEY, AND C. F. HAWKINS
(From the Department of Medicine, Birmingham University, and the Department of Clinical Pathology, Queen Elizabeth Hospital, Birmingham)

With Plate 9

SINCE the work of Thaysen (1932) and of Bennett, Hunter, and Vaughan (1932), reports on the syndromes associated with steatorrhoea, such as those by Hansen and Staa (1936), Hotz and Rohr (1938), and Snell (1939), have become more frequent. Thaysen considered that non-tropical sprue and idiopathic steatorrhoea were identical, and that coeliac disease was a manifestation of the same disorder in infancy. We have accepted this assumption and, though it is still not possible to explain the cause of steatorrhoea, suggest that a further review of the symptoms and signs of idiopathic steatorrhoea may be valuable.

Patients Investigated

From a series of more than 300 patients with a steatorrhoea, we have selected 100 who from long observation appeared to have idiopathic steatorrhoea and

TABLE I

Age of Patients when First Seen

Age (years)	0-20	21-30	31-40	41-50	51-60	61-70
Number of patients	7	13	27	27	16	10

thus to be suitable for the present study. None showed evidence of structural intestinal defects or other conditions such as tropical sprue, tuberculosis, regional ileitis, neoplasm, or amyloid disease. There are many difficulties in making the diagnosis, and many patients in whom a firm diagnosis has not yet been possible have been excluded. There were 49 men and 51 women, whose ages at the time they were first seen are given in Table I. This Table does not show the age at the onset of symptoms, as the patients were first seen when attending a hospital for adults. The period of observation of the surviving patients was two to ten years, averaging 5.2 years; during this time 14 patients have died.

Symptoms and Diagnostic Features

Presenting symptoms. One of three main groups of symptoms caused patients to seek medical advice.

1. *Constitutional disturbances* (44 patients). Lassitude, loss of weight, glossitis, and symptoms of anaemia were the main complaints, though many patients had

¹ Received March 27, 1952.

had loose stools for many years. In 18 of these patients diarrhoea had not been present at any time.

2. *Diarrhoea (43 patients).* This was usually severe, and will be discussed fully later.

3. *Miscellaneous symptoms (13 patients).* Two patients were seen on account of neurological symptoms simulating subacute combined degeneration of the cord, two had severe tetany, two were seen on account of severe backache, and

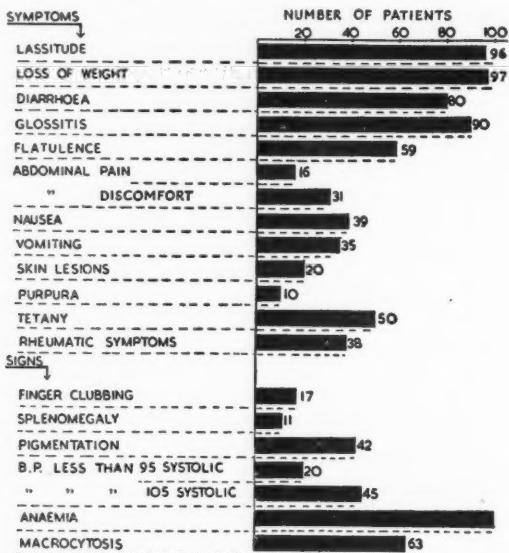


FIG. 1. Incidence of the main symptoms and signs in 100 patients with idiopathic steatorrhoea.

one owing to a fracture of the neck of the femur (see *Skeletal system*). The remainder had gastric symptoms suggesting ulceration. Two patients of this group had no diarrhoea.

Individual symptoms. The incidence of the individual symptoms occurring at any time while the patient was under observation is shown in Fig. 1.

Lassitude. This was the commonest symptom, and varied in severity, finding expression in many ways which are best illustrated by accounts given by some of the patients themselves. One patient (Case 17) stated that she always felt tired and became easily fatigued, so that on occasions she 'hardly knew how to return home'. Nevertheless, she was able to keep house for her brother and to complete large amounts of stage dressmaking, on a voluntary basis, which often necessitated long and late hours of concentrated work. A registered nurse (Case 24) never experienced more than mild intestinal upsets and moderate degrees of anaemia. Her principal complaint was of bouts of excessive weariness, lasting two to four weeks at a time, so that when off duty all she could do 'was to go to bed and sleep'. During such bouts she was able to carry out arduous

training duties in the wards and subsequently as a Staff Nurse of a leading London maternity hospital. Another patient (Case 23) had many interests besides her normal work, including Girl Guides and youth welfare activities. These she continued to perform, although feeling completely exhausted and having lost much weight before seeking medical advice. Lassitude is a subjective symptom incapable of any objective measurement, but its persistence, when diarrhoea had abated and anaemia had been corrected, suggests that this symptom is based upon the fundamental disturbance in steatorrhoea and therefore may have an organic basis. Further support for this suggestion was found in the rarity of neurotic symptoms. In spite of great physical weariness, the mental activity and initiative of these patients compared favourably with the normal.

Bowel habits. All but 20 patients suffered a disturbance of bowel habits. A common feature was attacks of loose stools, or actual watery diarrhoea, lasting for a few days three or four times a year. The stools were usually paler than normal, in most cases offensive, and sometimes frothy; occasionally the colour was normal. In many instances the onset of such episodes was sudden and was followed by numerous pale watery stools, sometimes associated with incontinence. In others the onset was more gradual, resulting in two to four semi-formed pale stools each day. These attacks were intermittent, but there was a further group of patients in whom the diarrhoea had begun many years previously and had persisted until their loss of weight and lassitude had brought them to seek medical advice. As Thaysen (1932) observed: 'Intestinal symptoms, especially diarrhoea, have persisted for years before this disease is diagnosed as "non-tropical sprue".' In such cases, where the patients have got accustomed to their diarrhoea and have lost interest in their disease, and where consulting physicians have not been sufficiently interested in the appearance of the stools so as to examine them by inspection, it is not to be wondered that the disease is not diagnosed before the diarrhoea is complicated with a severe degree of anaemia, glossitis, or extreme debility.' It was not only patients who had had loose stools for some years who made no complaint. Some with diarrhoea of recent onset were too preoccupied with their lassitude, loss of weight, and sore tongue to mention the presence of two or three loose motions daily, often not especially pale or offensive. As in other diarrhoeal conditions, long car journeys, spells of extra work, overtime in the factory, and excessive athletic exercise were found to be precipitating factors. In two patients the sudden onset of diarrhoea was related to severe mental disturbance: in Case 9 symptoms followed exposure to heavy aerial bombardment, and in Case 29 the loss of a husband killed in action. In both these patients there was evidence that the underlying defect had been present before the acute onset of the diarrhoea. In other patients business, financial, or domestic upheavals precipitated severe attacks. Rest in bed, on the other hand, usually produced a rapid cessation of diarrhoea, and sometimes even constipation. Over-indulgence in fatty and especially in fried foods was a common cause of loose stools, and was occasionally the starting-point of a severe attack: one patient (Case 5), who was especially

fond of dripping and toast, could usually manage one slice, but if she took two she would suffer severe diarrhoea a few hours later. Experience had taught many of our patients to avoid meat-fats and fried foods, without any impairment of their appetite for such articles of diet. Between the attacks more than 70 patients had normal bowel habits, and passed stools of normal colour and consistency once or twice a day. Fifteen tended to be constipated. Finally, it must be remembered that 20 patients, or one in five, at no time had any diarrhoea. The fact should also be emphasized that pale stools may occur in diarrhoeal conditions in which there is no steatorrhoea, and that frequently stools containing an excess of fat may be of normal colour and consistency.

Abdominal symptoms. Abdominal symptoms were usually mild, so much so that a description of them could often only be elicited by direct questioning. This was surprising, since the inconvenience caused by the diarrhoea would be expected to cause introspection. Flatulence or flatus was experienced at some time by more than half the patients. In Case 14 flatus was so marked and offensive that the patient felt 'he should be isolated', and another patient (Case 13) had become a heavy smoker in an attempt to counteract the unpleasant smell. Nausea occurred during attacks of loose motions in 39 patients, and vomiting in 35. Although the vomiting was usually associated with nausea, in some patients it occurred with little warning, and had been misdiagnosed as pyloric stenosis (compare Bassett, Keutmann, Hyde, Van Alstine, and Russ, 1939). Distension after meals was rarely troublesome, though the abdomen was frequently more prominent than in normal persons. Epigastric pain, of moderate intensity and related to meals, was encountered in eight patients, in four of whom it passed through to the back. In one (Case 27) there was no evidence of pancreatitis at autopsy. Severe abdominal pain is rare in idiopathic steatorrhoea, and was only encountered in two patients of this group. One (Case 1) had been under our observation for eight years when he developed abdominal distension after meals, later associated with abdominal pain of such severity that nausea and vomiting invariably occurred during the attacks. After the occurrence of borborygmi and defaecation the distension disappeared and pain ceased. Each attack lasted three to four hours. The clinical picture called for laparotomy to exclude any cause for intestinal obstruction. The operation revealed a dilated and redundant colon, and a diagnosis of partial volvulus secondary to gaseous distension of the colon was made. This group of symptoms gradually subsided with improvement in the patient's general condition, and for the past three years he has been quite well. Another patient (Case 28) was admitted with severe pain, vomiting, atonic distension of the gut, absolute constipation, and hypokalaemia, in association with small-intestinal diverticula. The severe abdominal pains ceased with the correction of the hypokalaemia. The patient, now aged 70 years, is well and active two years later, though still suffering from indigestion and occasional attacks of diarrhoea. Ingelfinger (1943) described a patient in whom the attacks also simulated intestinal obstruction, and in whom ileostomy was performed on three occasions, each time at a higher level, before the true nature of the underlying condition and the significance of the gaseous

distension of the gut was recognized. Mild colic, localized below the navel, was experienced by approximately 25 per cent. of our patients, but repeated and severe colic calls for careful consideration of the diagnosis. Proctitis and tenesmus were found in many patients in whom diarrhoea was troublesome. Both these conditions cleared rapidly with cessation of the loose motions.

Appetite. Dünner, Hirschfeld, and Gerald (1934) called attention to the excessive appetite, and Hotz and Rohr (1938) also laid stress upon this symptom. Thaysen (1932) considered that the appetite was usually lost, though he too noted a few patients in whom it was excessive. In the present series a good appetite was the rule, and some patients had an excessive appetite even when losing weight. One patient, for example (Case 27), stated that the feeling of 'never being able to eat enough' was his most troublesome symptom, for if he ate to repletion his diarrhoea was aggravated. Rarely was any difficulty experienced in providing food to the patients' liking, but in particularly severe attacks of diarrhoea appetite was sometimes lacking.

Loss of weight. Thaysen (1932) noted an average loss of 18 kg., varying from 26 to 2.2 kg., in nine patients. He also commented upon the great variation in weight of these patients in the absence of any noteworthy change in blood count or bowel habits. Snell (1939) reported an average loss of 30 lb., the greatest being 70 lb. All except three of our patients had lost weight at the time they sought advice, either gradually for two or three years or relatively quickly for a few months. The decrease in weight was invariably associated with loss of energy, but did not bear any definite relationship to the frequency or consistency of the stools. The average loss at the time of first examination in the 83 patients above the age of 25 years was 28.3 ± 17.09 lb. (range 0 to 84 lb.). A high mortality occurred among those with the greatest loss of weight.

Cramp and tetany. The association of tetany with this disorder has been recognized for many years. Snell (1939) noted the occurrence of tetany in nine of 32 patients, and Bennett, Hunter, and Vaughan (1932) commented upon its occurrence in the absence of diarrhoea. Only two of our patients presented with tetany; in one bowel action was normal, and in the other frequent. Two further patients had attacks of tetany while in hospital, with severe pain, shock, and muscle spasm lasting for three days in spite of treatment. Cramps occurred at some time in practically every patient; they were usually mild and transient, and not necessarily associated with diarrhoea.

Haemorrhagic disorders. Thaysen (1935) described in one patient severe bleeding from the bowel, and later spontaneous subcutaneous haemorrhages, which he ascribed to deficiency of vitamin C. Holst (1927) published the post-mortem findings in a woman who died as a result of a massive haemorrhage into the jejunum. Golden (1945) also noted the occurrence of recurrent severe intestinal haemorrhages in one patient, but at autopsy only advanced atrophy of the intestinal tract, and no source of haemorrhage, could be found. Haemoptysis and haematuria occurred in a patient reported by Collins and Hoffmann (1943), in whom the prothrombin time was prolonged, but the effect of sulphasuxidine could not be excluded. Alper (1942) described recurrent haemarthroses. The commonest

haemorrhagic manifestations are those in the skin and subcutaneous tissues. The occurrence of petechiae has been described by Hotz and Rohr (1938), Holmes and Starr (1929), Meyer (1932), and Snell (1939), and both Thaysen (1932) and Hansen (1938) recorded bleeding from mucous membranes. Although such manifestations are usually trivial, Kark, Souter, and Hayward (1940) have described extensive confluent subcutaneous lesions. Ingelfinger (1943) reported a patient who presented with haematuria, which was ascribed at first to a tuberculous lesion, but three days later the patient bled from the nose and mouth and large areas of purpura appeared. The condition was associated with a prothrombin deficiency, and rapidly responded to vitamin-K therapy. In the case reported by Bassett, Keutmann, Hyde, Van Alstine, and Russ (1939) haemorrhagic manifestations in the skin and in the urinary and intestinal tracts were preceded for a few days by swellings of the joints. In our series purpura occurred in 10 patients. In five there was no diarrhoea at any time, and in two of these purpura was the presenting symptom. In six patients the lesions varied from one or two millimetres in diameter to large confluent areas, and in five cases were associated with swellings of the joints. Severe haematuria occurred in Case 4, and haemorrhage from the bowel in Case 97.

Personality characteristics and associated symptoms. Many of the early writers have commented upon the frequency of mental symptoms such as depression, paranoia, Korsakov's syndrome, and neurasthenia. The majority of such observations, however, were made towards the end of the illnesses, when the effects of dehydration, electrolyte loss, and protein starvation might produce mental changes. In our experience headaches, giddiness, palpitations, shortness of breath, praecordial pain, and other symptoms so often associated with anxiety states were rarely encountered. The number of patients in whom induced symptoms have occurred is negligible, in spite of the fact that the whole group of patients has been under intensive investigation for many years. The querulous, fractious state of the patient severely ill with coeliac disease or sprue was only seen in two patients. In these two the appetite and dietary likes and dislikes varied from meal to meal, so that only with difficulty could a meal be produced that was acceptable in every respect. Four patients had considerable emotional difficulties connected with domestic affairs. Two of these, Cases 26 and 32, appeared to use their underlying organic disorder as an escape mechanism. Mention has already been made of the role of emotional upsets in precipitating attacks of diarrhoea, but it is doubtful whether such events are more frequent in these patients than in the general population. Nevertheless, it is of interest that 10 of our patients had previously been diagnosed as suffering with 'nervous diarrhoea'. Two patients required psychotherapy. One (Case 5) had episodes of hypokalaemia with mental confusion, and later, after apparent restoration to normal health, involutional melancholia: another (Case 62) had periods of severe depression. Taking the group as a whole, the majority had come to terms with their disability, learning to avoid those actions and articles of food which aggravated their symptoms. The patients appeared to have a fairly high level of intelligence, and to be energetic both in mind and body,

cheerful, and not introspective. In these latter respects they contrasted noticeably with patients suffering from ulcerative colitis.

Glossitis. Glossitis occurred in 32 of 47 cases recorded by Thaysen (1932), and in 24 of 32 cases reported by Snell (1939). It was present at some time in 90 of our 100 patients. In approximately one-third the symptoms caused were severe, while in one-third they were never more than mild and transitory. There were no diagnostic features by which the lesions could be differentiated from those occurring in other nutritionally deficient states (Jolliffe, 1950). In the most severe examples the whole tongue and the inside of the mouth were fiery red, usually with multiple areas of ulceration of the buccal mucous membranes and edges of the tongue. In the mild forms the tip and edges of the tongue presented a smooth, bright red, and sore surface. On other occasions aphthous ulcers, with little if any glossitis, were the chief feature. Sometimes the only residual evidence of previous glossitis was a normal-coloured tongue pitted along the edges with marks of the teeth. During long periods of observation mouth lesions varied from time to time both in their clinical manifestations and in their response to treatment. When the oral condition became chronic the tongue was smooth, glazed, redder than normal, and without normal papillae. It rarely simulated the pale, smooth tongue usually seen in pernicious anaemia. The onset of glossitis may be extremely rapid. In Case 24 soreness first appeared, followed by a diffuse red-brown erythema of the palate, fiery redness of the tongue, and numerous buccal and tongue ulcers, in the course of 48 hours. Reactivation of oral lesions was often associated with deterioration of the general condition, loss of weight, and recurrence of diarrhoea. In seven patients exacerbation was related to menstruation. In many patients, however, glossitis appeared quite independently of such changes, and for no very evident reason. Cheilosis was encountered in only four, but angular stomatitis in approximately half of the patients. Other mucous membranes were affected. In six cases the glossitis was accompanied by dysphagia. This was so severe as to cause marked restriction of food intake, and was probably due to extension of the epithelial involvement to the pharynx and oesophagus. For obvious reasons we have not examined the stomach by gastroscopy during acute attacks, but in three patients examination during quiescent periods showed appearances similar to those reported in pernicious anaemia (Schindler and Serby, 1939). Five patients had perianal excoriation and soreness together with the glossitis. Dyspareunia was noted by four other patients.

Hypokalaemia. In diarrhoea due to any cause there is an increased excretion of electrolytes in the faeces. In some patients with steatorrhoea this loss may continue even in the absence of watery stools, and we have found that as much as 2 gm. of potassium daily may be lost in this way. It is not surprising, therefore, that patients with the steatorrhoea syndrome readily become depleted of sodium, potassium, and water as the result of relatively minor disturbances of bowel habit. Ten cases of varying degrees of deficiency were diagnosed and successfully treated. In the mild cases complaints of weakness and 'heavy' limbs, together with mental apathy and rapid loss of weight, were noted. That

such complaints were specifically related to potassium deficiency was proved by the demonstration of a serum-potassium less than 3.5 mEq per litre, and by the removal of symptoms and rapid replacement of weight on the administration of potassium. Recent attacks of diarrhoea were the most common precipitating factors, but these mild manifestations also occurred without obvious alteration in bowel habit. In five severe cases loss of weight was greater and more rapid, blood-pressure low (70 to 80 mm. Hg systolic), reflexes absent, and muscle weakness profound, and mental apathy and personality changes were prominent. The abdomen was distended, simulating ileus, and vomiting caused further loss of potassium. Recognition of the importance of potassium therapy enabled us to restore to full working life a few patients whom our previous experience would have adjudged too severely ill to recover.

Onset in childhood. Thaysen (1932) found that approximately half of his patients had a history of acute or chronic intestinal disease in infancy or childhood, and our experience has been similar. Of the 100 patients there were 43 in whom the onset of the disorder in childhood is inferred from the occurrence of severe diarrhoea, anaemia, 'tuberculous peritonitis' or 'consumptive bowels', or from hospital diagnosis. For example, a patient (Case 12) was first seen at the age of 53 years on account of two years' severe anaemia with diarrhoea. He was later found to have suffered so severely with feeding difficulties and intestinal disturbances from the age of two to the age of five years that his life had been despaired of. A woman aged 50 years (Case 17) had had loose stools since she was 12 years old. Until that age she had developed normally, but after the onset of diarrhoea she ceased to grow, and her height remained unchanged at 4 ft. 11 in. A woman of 21 years (Case 2) developed anaemia and glossitis. It was found that at the age of 9 years she had had an illness with diarrhoea, which lasted 13 months and caused her weight to fall to 3 stone. After a 'cure with daily chicken's liver and eggs' she recovered, and ever since she has tended to be constipated.

Sexual characteristics. In the majority of patients the menarche and meno-pause occurred at the normal times, and menstrual irregularities were not common. In 41 patients the average age at the onset of menstruation was 14.8 (range 12 to 19) years, and in 18 patients the average age at the meno-pause was 45 (range 35 to 53) years. Pregnancy had no ill effect, and occurred even in patients in whom a mild macrocytic anaemia and fat-absorption defects were still present. Though complete data are not available, three of our patients complained of impotence. Nevertheless, virility was maintained in spite of moderately severe constitutional disturbance. Of the 32 married female patients seven were childless, and the remainder produced 50 children; of the 38 married men 11 were without offspring, and the remainder had 57 children.

Family history. Thaysen (1932) at first denied the likelihood of steatorrhoea in siblings, but later (1935) reported the cases of a brother and sister, whose mother was also probably affected. Hotz and Rohr (1938) found coeliac disease in the daughter of one of their patients, Kessler (1937) in a mother and son, and Fanconi (1928) in four members of a family, two of whom were twins. Evenson

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(1936) also reported twins with coeliac disease, and Meyer (1932) observed sprue and coeliac disease in one family. Davidson, Girdwood, and Innes (1947) found five members in one family who suffered from idiopathic steatorrhoea. More recently Davidson and Fountain (1950) have shown a high familial incidence in coeliac disease as the result of a familial predisposition to the disorder. In our series 10 families have been found in which the presence of steatorrhoea was

TABLE II

A. Families in which Steatorrhoea has been Confirmed in More than One Member

<i>Family</i>	<i>Numbers confirmed</i>	
I	3	Case 1 nephew to Case 37 (male) and cousin to Case 84 (female). His brother had macrocytic anaemia and loose stools at 16 years of age
II	2	Case 16 brother of Case 17 (female)
III	2	Case 7 brother of Case 79 (female)
IV	2	Case 34 mother of Case 36 (male)
V	2	Case 40. Her sister has ileocolitis. A brother had anaemia and skeletal deformities in childhood
VI	2	Case 57. Grandfather of a boy diagnosed as having coeliac disease at another hospital
VII	5	Case 60 brother of Case 67 (female) and uncle of Cases 68 and 66 (females). A brother has atypical macrocytic anaemia and borderline fat-absorption defect. Another brother died of 'pernicious anaemia' aged 29 years. One nephew has regional ileitis
VIII	3	Case 63 (female). Her son has coeliac disease; her mother has idiopathic steatorrhoea. A brother has 'pernicious anaemia'
IX	2	Case 73 (male). His son has coeliac disease
X	6	Case 91 (male). Father, aunt, sister, nephew, and niece are all affected

B. Families in which More than One Member has Possibly been Affected

I	Case 33 (male)	Sister has anaemia and 'colitis'
II	Case 38 (female)	Sister has iron-resistant anaemia and diarrhoea
III	Case 11 (female)	Mother had severe anaemia and recurrent diarrhoea
IV	Case 39 (female)	Mother has severe 'colitis' and anaemia
V	Case 56 (male)	Mother died of 'colitis', with similar symptoms, at 40 years of age

Total number of families in the series, 92.

confirmed in more than one member. In five further families there was a strong possibility of a similar occurrence (Table II). The more completely the blood-relatives of patients with idiopathic steatorrhoea are investigated, the stronger does the evidence of a familial incidence appear.

Associated diseases. Hansen and Staa (1936) were impressed with the frequency of systemic neurological disorders in their patients, whereas other reported series and our own experience lend no support to their tentative suggestions. Among our patients there were few who had suffered from any major illness except rheumatism; six had rheumatic heart disease, and five others had been diagnosed elsewhere as having had rheumatic fever. Five further patients, in addition to those in whom joint manifestations were associated with purpura, suffered from recurrent swellings of a rheumatic type in the knees and ankles.

Such a proportion of patients with this type of rheumatism is larger than would be expected in the normal population. In view of the comment by Hurst (1942) that 'obstruction of the lacteals by tuberculous glands is the cause of the majority of cases of non-tropical sprue', particular attention was paid to the incidence of tuberculosis in our group of patients. Five showed evidence of either active or healed tuberculosis. One patient (Case 47) suffered a pleural effusion one year after coming under our observation, and X-ray examination three years later disclosed a number of calcified foci in the right lung. Another (Case 35) had healed tuberculosis at the apex of his right lung, and his brother had died of pulmonary tuberculosis. Another (Case 5) suffered a recrudescence of tuberculous cervical adenitis necessitating operation. Another (Case 21) died elsewhere of pulmonary tuberculosis, though when she was first seen an X-ray of the chest was normal. One patient (Case 78) developed active pulmonary tuberculosis, with cavitation and haemoptysis, while under close clinical and radiological supervision. He made satisfactory progress with sanatorium treatment, but died of a coronary thrombosis. Autopsy showed that the cavitation had healed completely, but that there was no evidence of intestinal tuberculosis. Four other patients had a strong family history of tuberculosis, but in none could a lesion be found: the father, mother, and sister of one (Case 19), the husband of another (Case 2), and brothers of two patients (Cases 22 and 34) had all died of pulmonary tuberculosis. In addition, the sister of Case 34 had died of 'Addison's disease'. On the other hand, no evidence of tuberculosis was obtained in any case which came to autopsy. In our view the illness of our patients was not primarily due to the tubercle bacillus, though occasionally the terminal events may be entirely those of tuberculosis (Case 21). A high incidence of tuberculous infection seems probable in a disorder in which malnutrition is so often present.

General appearance and examination. The mean height of the male patients was 65.7 ± 3.04 inches, and of the female patients 61.86 ± 3.48 inches, and was thus slightly less than that of the normal population. Many of the patients had a characteristic physiognomy. Bennett, Hunter, and Vaughan (1932) called attention to the rather plump and round face with prominent zygomatic arches. This description applies to female sufferers, and was present in 18 of our patients. There are, however, male characteristics, in which the forehead is somewhat wider than usual and the jaw rather narrow, giving the face a triangular appearance from the front, though the profile remains normal (Plate 9, Fig. 3; compare Hotz and Rohr (1938), Cases 2 and 14; Bennett, Hunter, and Vaughan (1932), Case 6). It is of interest that we have not as yet discovered idiopathic steatorrhoea in a patient with black hair, and only two have had dark brown hair. Premature greying of the hair was common, and might occur long before any other symptom. The hair itself was invariably of fine texture. In the men the beard grew poorly, shaving being necessary only two or three times a week. In some the axillary hair disappeared, but in spite of the poor growth of hair generally seen, baldness was not encountered.

Pigmentation and skin rashes. Generalized pigmentation closely resembling

Addison's disease was seen in 10 patients. Indeed, with the associated hypotension and a low serum-sodium, the correct diagnosis may easily be missed. A further 32 patients had pigmentation of the extensor surfaces of the arm, neck, and face, with a contrasting pallor of the palms. On account of its distribution we have termed this pigmentation 'pellagroid'. During the summer months patients often developed coincidentally a parchment type of epithelium and cracking on the extensor surfaces of the arms, but formation of bullae and desquamation were not encountered. In 20 patients of the series a desquamating rash affecting the hands, legs, and forearms, and occasionally the face, was encountered, and in 10 it had been diagnosed as seborrhoeic dermatitis at a previous attendance at a skin clinic. Of special interest was a rash similar to psoriasis seen in six patients; in four the rash occurred during an exacerbation of the systemic disease, and was related to the phasic variations characteristic of idiopathic steatorrhoea.

Clubbing and koilonychia. Clubbing of the fingers occurred in various degrees and at various times in 17 of our patients. It was reversible, and might appear or clear up relatively quickly, and accurately reflected the general physical state of the patient. In our experience clubbing has been less common in idiopathic steatorrhoea than in fat-absorption defects due to other causes. Consequently we have taken this sign as indicating a thorough search for any other possible cause before accepting the diagnosis of idiopathic steatorrhoea. Koilonychia was seen in seven patients, and responded satisfactorily to iron therapy.

Pyrexia. Fever may occur in idiopathic steatorrhoea (Thaysen, 1932). We found that in many patients an occasional rise of temperature to 99° to 100° F. occurred. A higher and more prolonged pyrexia occurred in five patients, in two of whom the possibility of enteric fever was seriously considered. Complete investigations, and the subsequent course, failed to reveal any other condition than steatorrhoea, and the pyrexia subsided in every patient with an improvement of the general condition.

Oedema and ascites. Oedema was frequently seen when the general condition was poor. Thirty-four patients at some time had oedema involving the dependent parts and not associated with congestive failure. In the group as a whole there was no correlation between the oedema and the level of the serum-proteins; in two patients oedema coincided with severe anaemia.

Cardiovascular system. Many workers have called attention to the low blood-pressure which is almost invariable. Snell (1939) found a systolic pressure greater than 110 in only five of 22 patients in whom the blood-pressure was noted. Our experience has been similar. Three patients had blood-pressures of 180/94, 170/100, and 160/100 respectively; 45 had systolic pressures of 105 or less, and 20 of these had systolic pressures of 95 or less. The lowest blood-pressure observed was 70/30 in a patient who was not especially ill or anaemic, and who eventually attained normal health and ability to work without undue fatigue. Low blood-pressures were usually found when the patients were first seen, and even on their recovery and return to normal life the pressures tended to remain low, only rarely rising more than 10 mm. Hg (systolic) above the

initial levels. In the fatal cases there was a progressive fall of blood-pressure with the gradual deterioration of the general condition.

Pulmonary system. Excluding those with tuberculosis, 10 patients were found to have a fine fibrosis of their lungs on X-ray examination, but as they all lived in an industrial city, where chronic lung disorders are common, the significance of the finding must remain doubtful. Any patient with bronchiectasis in whom the pancreatic enzymes had not been studied was automatically excluded. In one patient (Case 73) who had segmental bronchiectasis the enzymes were normal.

Abdomen. Many patients had a 'doughy' abdomen, which might easily be mistaken for a sign of tuberculous infection. The liver was not enlarged, but mild splenomegaly was present, in 11 patients. Sigmoidoscopy was not performed as a routine, but in 12 patients the mucosa was hyperaemic and bled easily, though none had ulceration or excess of mucus.

Central nervous system. Lesions of the central nervous system in idiopathic steatorrhoea were rare in the present study. Two patients had absent reflexes, extensor plantar responses, and absent vibration sense, but both had free acid in the gastric juice. They had been bedridden when first seen, but after a short period of treatment became fully ambulant. A few patients had diminished reflexes which appeared to be the result of electrolyte disturbances rather than manifestations of peripheral neuritis. These signs disappeared with improvement of the general condition.

Skeletal system. Decalcification has been emphasized in all previous reports, and bone changes were especially noticeable in the series of patients reported by Bennett, Hunter, and Vaughan (1932). The skeleton was not X-rayed as a routine in the present series. Four patients have suffered spontaneous fractures. A woman of 50 years (Case 39), who had previously been diagnosed as suffering from colitis, complained of severe rheumatism. Examination revealed that 12 ribs were fractured, and there were spontaneous fractures in both scapulae. A woman of 30 years (Case 31) had a pseudo-fracture of her right ulna. The remaining two patients, aged 16 and 20 years, began to limp; one had a fracture of the ramus of the pubis, and the other a crack in the neck of the left femur. Of the remaining patients who have been X-rayed approximately two-thirds have shown some evidence of decalcification, but apart from a few who complained of persistent backache they had no symptoms referable to this finding.

Radiology of the intestinal tract. Much has been written about the radiological pattern of the intestinal tract in idiopathic steatorrhoea (Snell and Camp, 1934; Kantor, 1939; Golden, 1945). Seventy-five patients of the present series have been examined with a flocculating barium emulsion (Ardran, French, and Mucklow, 1950), and all showed varying degrees of a deficiency pattern. Some of our earlier patients did not have this investigation, but our subsequent experience has led us to regard radiological examination of the intestinal tract as an integral part of the study of any patient suspected of steatorrhoea. Although there was, on the whole, some correlation between the degree of

flocculation and the severity of the fat-absorption defect, there were exceptions. In the majority of patients examination by barium enema failed to show any abnormality; occasionally the colon appeared elongated and dilated, and in rare cases it resembled a true megacolon (Bennett, Hunter, and Vaughan, 1932).

Haematology. When first seen two-thirds of the patients had macrocytosis, usually associated with an increased mean cell-volume. In a few whose mean cell-volume was within the normal range, the presence of macrocytosis was established by a Price-Jones curve. It has been shown that the lack of correlation between cell-diameter and cell-volume is due to the frequency with which the erythrocytes are found to be thinner than normal. For the same reason microcytosis was very rarely seen even in patients who had a severe hypochromic anaemia; in fact, cases of considerable iron deficiency were found in which the mean diameter was increased. The common picture encountered in such cases was a mixture of large and normal-sized erythrocytes with much variation in depth of staining (Bennett, Hunter, and Vaughan, 1932). Of the patients who showed obvious macrocytosis a small number had a peripheral blood picture which was indistinguishable from that of pernicious anaemia. The usual appearances, however, in the stained films were a moderate degree of anisocytosis with conspicuously little poikilocytosis and occasional target cells (Cooke, Frazer, Peeney, Sammons, and Thompson, 1948). The sternal marrow was examined in 49 patients, and all showed some degree of erythroid hyperplasia. In 17 patients erythropoiesis was both orthoplastic and dysplastic. In some instances the normoblasts showed evidence of premature haemoglobinization and were large in size. This abnormal form of erythropoiesis predominated in 21 further patients in whom typical megaloblasts were not seen. The remaining 11 patients showed no significant abnormality. There appeared to be some correlation between the severity of the anaemia, in terms of the red-cell count, and the type of erythropoiesis. All patients in whom megaloblasts were seen had erythrocyte counts below 2.9 million per c.mm., while the lowest peripheral count in which atypical erythropoiesis occurred without megaloblasts was 2.3 million per c.mm. Severe anaemia was not common, the red-cell counts usually being between 3 and 3.5 millions per c.mm., with haemoglobin levels between 11.4 and 13.1 gm. per 100 ml.

Faeces. The demonstration of steatorrhoea is the keystone of diagnosis, and the methods adopted have been detailed elsewhere (Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946). Usually a single three-day balance test was adequate for diagnosis, but when the defect was slight or the patient was constipated repeated three-day tests were carried out. The mean fat absorption on the initial examination of our patients was 74.8 ± 12.25 per cent. (range 30 to 89 per cent., median 80.5 per cent.). Microscopic examination of the faeces showed an excess of fatty-acid crystals in 85 patients.

Plasma. The plasma failed to show any features diagnostic of steatorrhoea, and the findings depended primarily on the state of nutrition and hydration of the patient rather than on the degree of fat-absorption defect. For this purpose the levels of sodium, potassium, calcium, and proteins gave most information.

Serum-sodium showed great variation, sometimes being as low as 276 mg. per 100 ml. (120 mEq per litre), a finding which might suggest Addison's disease. Serum-potassium was not estimated as a routine until recently, when it became evident that low values of 2.5 to 3.0 mEq per litre were not uncommon. The serum-proteins were determined in 70 patients; in five the total proteins were less than 5 gm. per 100 ml., and in seven the serum-albumin was less than 3.5 gm.

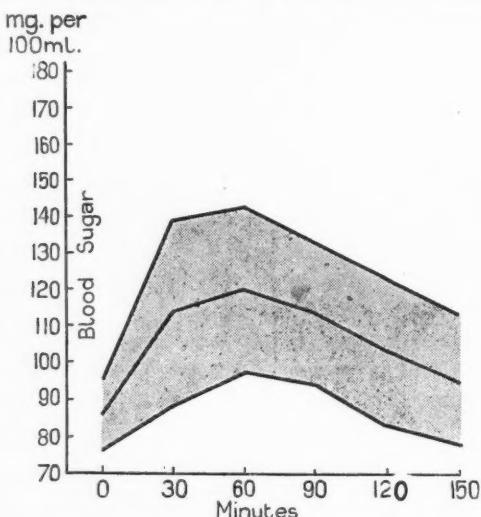


FIG. 2. Oral glucose-tolerance tests in 72 patients, showing the mean curve and standard deviation.

per 100 ml. In the remaining patients the values were normal. Total plasma-cholesterol values were low in many cases, but the deficiency was more closely correlated to the degree of anaemia than to the severity of the steatorrhoea; the mean value in 50 patients was 201 ± 70.6 mg. per 100 ml. The ratio of free to ester cholesterol, with few exceptions, was normal. The results of colloidal-gold, thymol-turbidity, and cephalin-cholesterol tests were collectively abnormal only in seriously ill patients. Partition chromatography showed an increased aminoaciduria in 16 patients out of 50 so investigated. A glucose-tolerance test following the oral administration of 50 gm. of glucose was carried out in 72 patients; the results are plotted in Fig. 2. There was no correlation with the degree of the fat-absorption defect or with the clinical condition.

Pancreatic enzymes. Duodenal intubation was carried out in 34 patients, and the values for amylase, lipase, and trypsin were all within normal limits. Comfort, Dornberger, Wollaeger, and Power (1949) reported similar findings. Secretin was not administered.

Diagnostic Criteria and Conclusions

In considering the patients under review we have been influenced by the absence of relevant pathological findings at autopsy in nine patients, and by the

similarity of the signs and symptoms in these fatal cases to those found in the other patients of this series, many of whom have now been observed for several years. We consider that the group under review presents a clinical picture which is sufficiently homogeneous, and sufficiently distinct from that of steatorrhoea due to demonstrable causes, to be regarded as idiopathic in type. We feel also that the data collected permit us to make some observations on the means of diagnosing idiopathic steatorrhoea. The only criterion we adopted in the early part of this study was the presence of steatorrhoea in the absence of a demonstrable aetiological factor. The gross appearance and microscopical examination of the faeces may be highly suggestive, but the only conclusive method available at present is fat-balance studies. Most workers consider 90 per cent. as the lower limit of normal absorption, and in this clinic the mean absorption in normal controls is 94.6 ± 1.9 per cent. Balance techniques are open to criticism, since they are liable to technical errors of ingestion, collection, or estimation. Fortunately, these errors usually accumulate to underestimate the amount of fat in the stools, so that any defect of absorption shown by balance techniques can be considered real. It is difficult to understand why a patient who absorbs 85 to 87 per cent. of ingested fat should have symptoms of the steatorrhoea syndrome, whereas one who absorbs 90 per cent. or more is unlikely to have such symptoms. Equally perplexing is the occurrence of identical conditions, such as refractory anaemia, in two members of a family, with the difference that one has a normal fat absorption while the other absorbs only 80 to 85 per cent. It may be that steatorrhoea is merely one aspect of a general disorder, and is subject to periodic variations. It is important to emphasize the fact that balance tests are a bulk measurement of the absorption of many different fats, and do not accurately show the proportions of particulate and fatty-acid absorption from the intestine, or indeed whether fats are being absorbed in their normal chemical form. In spite of these limitations, fat-balance tests must remain the mainstay of diagnosis until more informative tests are devised.

In making a diagnosis of idiopathic steatorrhoea it is clear, however, that other criteria must be carefully weighed. Two-thirds of our patients had macrocytosis when their blood was first examined, and the remainder developed an increased mean cell-volume at some time while under our care. Therefore in this clinic we have come to regard persistently normal blood values as a strong evidence against the diagnosis of idiopathic steatorrhoea. On the other hand, a normochromic macrocytic anaemia in which poikilocytosis is not conspicuous, or even a hypochromic anaemia in which there is considerable variation in depth of cell-staining, is extremely suggestive of the presence of steatorrhoea. In many patients these features have been the first clue to the correct diagnosis. There is a close resemblance between nutritional macrocytic anaemia, as defined by Darby and Jones (1950), and idiopathic steatorrhoea as we conceive it, and it seems likely that the diagnosis offered in any given case will depend upon whether the emphasis is on the anaemia or on the fat-absorption defect. In emphasizing the value of haematological changes in the diagnosis of idiopathic

steatorrhoea, it should be stated that there are other conditions, not specifically associated with steatorrhoea, which may show similarities in the blood picture to the cases under discussion. These include kwashiorkor, tropical macrocytic anaemia, and disturbances of liver function, and such conditions are probably associated with defects of protein intake or utilization rather than with defects of fat absorption. Owren (1950) has claimed the isolation from liver of a protein-synthesizing compound, which is necessary in both pernicious anaemia and idiopathic steatorrhoea before macrocytosis is corrected and normal haemoglobin formation resumed. Though the role of the liver in all these conditions is by no means clearly defined, the similarities in the blood picture, the frequent finding of excessive aminoaciduria, and the beneficial effects of increased protein intake in idiopathic steatorrhoea suggest the possibility that the anaemia may be due as much to disturbed liver function as to a failure of absorption of specific haematinic substances.

Radiography of the intestinal tract must be accepted as an essential diagnostic procedure. It is our practice to carry out this investigation with a flocculating barium emulsion, and we have found a 'deficiency' pattern in all the patients. Consequently we have come to regard this sign as one of the diagnostic criteria, as was originally suggested by Snell and Camp (1934). Thus, if it is not possible to perform a fat-balance test, the demonstration of a deficiency pattern, together with suggestive symptoms, an abnormal blood picture, and an excess of fatty-acid crystals in the faeces, makes the diagnosis of idiopathic steatorrhoea almost certain. Since, however, regional ileitis and jejunio-ileitis may closely resemble idiopathic steatorrhoea, additional information may be obtained by the use of a non-flocculating barium emulsion, by which strictures or abnormal mucosal patterns may be more clearly delineated. It is customary to include a low result from the oral glucose-tolerance test among the diagnostic criteria, and in many patients a tolerance curve with a rise of less than 40 mg. per 100 ml. is found. French, Thomas, and Thompson (1951) have shown that this delayed absorption curve cannot be explained by delay in gastric emptying, and have inferred that there is a definite impairment of absorption of glucose from the intestinal lumen. The level of the blood-sugar, however, depends upon many factors, among which may be the rate of deposition of glycogen in the liver and muscles and also its rate of mobilization. Unless these factors are known—and there is as yet no satisfactory evidence upon these points—deductions that impairment of absorption is the main factor causing a low tolerance curve are not beyond criticism. While many patients with idiopathic steatorrhoea admittedly have a flat tolerance curve, it is by no means invariable. We have confirmed this fact in patients in whom the diagnosis was verified at autopsy, and for this reason we do not emphasize the glucose-tolerance test as a diagnostic criterion.

Two important questions remain to be considered, namely, the value of the determination of the pancreatic enzymes and the differential diagnosis of idiopathic steatorrhoea from pancreatitis. Thaysen (1932) found that pancreatic enzymes were normally present in idiopathic steatorrhoea, but until Anderson's work (1938) on fibrocystic disease of the pancreas focused attention on the

possible value of such investigations, few other observations were made. Comfort, Dornberger, Wollaeger, and Power in 1949 found normal values for amylase, lipase, and trypsin in 13 patients with idiopathic steatorrhoea, and observations in the present series support these findings. It may therefore be admitted that these three enzymes are normally present in this disorder. Duodenal intubation was not performed in many of the patients included in the present series, and it might be objected therefore that there is no justification for applying the diagnosis of idiopathic steatorrhoea to them. But their clinical similarities to the patients in whom the pancreatic enzymes were demonstrated were close enough to be regarded as manifestations of the same disorder. As Comfort, Dornberger, Wollaeger, and Power stated, there are many points of clinical difference between pancreatitis and idiopathic steatorrhoea which are so pronounced as to make the time-consuming and inconvenient procedures of duodenal intubation and the secretin test unnecessary for diagnostic purposes. Although we agree with this observation, which permits a diagnosis to be made, it leaves many questions unanswered. As Comfort and his colleagues pointed out, a transitory disturbance of pancreatic function may be expected to occur in sprue because of its nutritional, metabolic, and electrolyte disturbances. There is also the possibility of patients developing a permanent loss of enzymes as a result of pancreatitis secondary to an intestinal disorder. This occurrence has been reported in ulcerative colitis (Ball, Baggottoss, and Bargen, 1950) and might be suspected in idiopathic steatorrhoea from some of the autopsy reports on that condition. In such cases it may not be possible to reach a completely accurate diagnosis. Clarification must await long-term studies with improved enzyme analysis and collection techniques, for the possibility cannot completely be excluded that the pancreas may hold the essential clue.

If to the finding of steatorrhoea, haematological changes, and radiological abnormalities there are added the main symptoms described in the present paper, a definite clinical syndrome emerges, characterized by mild chronic ill health subject to relapse and remission, recurrent glossitis, mild anaemia, and variable degrees of intestinal upset. Our experience, therefore, in this clinic has led us to believe that idiopathic steatorrhoea presents a clinical picture which is easily recognizable when one is alert to it. It may simulate many other diseases before the correct diagnosis is reached. From the haematological aspect, no case of refractory macrocytic anaemia, achrestic anaemia, or atypical pernicious anaemia can be considered satisfactorily investigated without a fat-analysis of the stools; this principle also applies to the rare types of iron-deficiency anaemia which fail to respond to oral iron therapy (Hawkins, Peeney, and Cooke, 1950). In the study of patients with diarrhoea the assessment of small-intestine function is often neglected, for many of our cases have been found among those hitherto diagnosed as mucous colitis, lienteric diarrhoea, 'colitis', or nervous diarrhoea. We now regard all these diagnoses as ill-sustained until fat absorption has been shown to be normal. To conclude this review, certain features have impressed us: the frequency of mild ill health among these patients, the number who were not complaining primarily of intestinal upset,

the high familial incidence, and the tendency for the variations in severity of both the principal symptom (lassitude) and the anaemia and glossitis to be dissociated from the variations of intestinal upset. These features suggest to us that the disturbance of intestinal function may be a reflection of a more generalized systemic disturbance rather than the primary cause of the disorder.

It is a pleasure to thank the physicians of the United Birmingham Hospitals for their kindness in referring patients to us, and especially Professor T. L. Hardy for his interest throughout this study. We are also greatly indebted to Mr. Garfield Thomas, of the Queen Elizabeth Hospital, for numerous biochemical investigations. We also thank Dr. Margaret Thompson, Dr. J. M. French, and Dr. H. G. Sammons, of the Department of Pharmacology, Birmingham University (Professor A. C. Frazer), for the majority of the pancreatic-enzyme determinations.

Summary

1. The symptoms, signs, and diagnostic features of 100 cases of idiopathic steatorrhoea are described. The findings are based on observations made during the past 11 years.
2. Idiopathic steatorrhoea is characterized by mild chronic ill health, recurrent glossitis, anaemia, and variable degrees of intestinal upset. There is a significant familial incidence. Diagnostic criteria include abnormal fat absorption as demonstrated by fat-balance techniques, disturbances of the haemopoietic system, and a 'deficiency' pattern on X-ray examination of the intestinal tract.
3. Patients with atypical anaemias or chronic diarrhoea cannot be considered as fully investigated unless a fat-absorption test has been performed.

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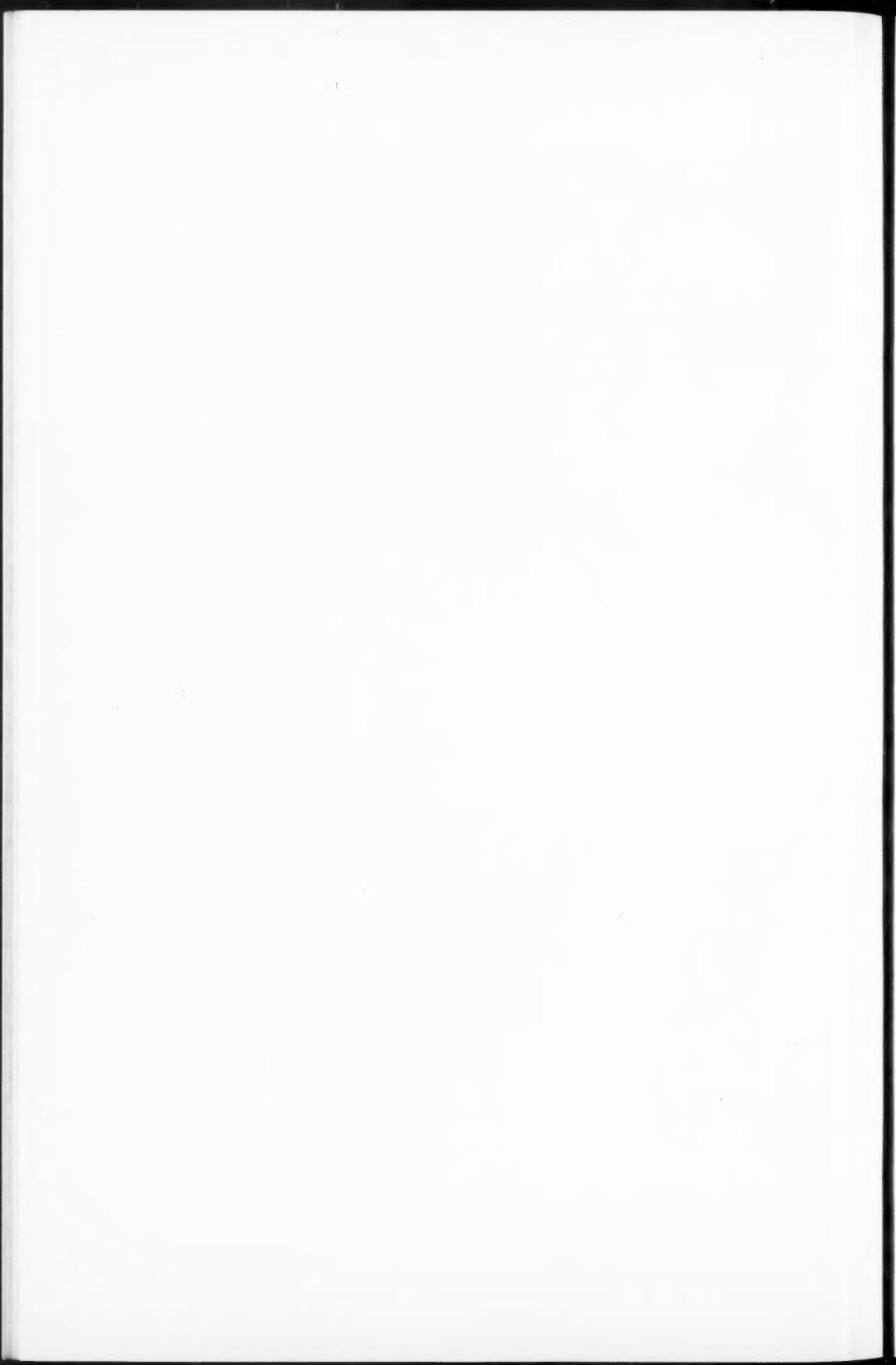
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FIG. 3. Three patients showing the 'triangular' shaped facies common in male patients with idiopathic steatorrhoea



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ATYPICAL CONGENITAL HAEMOLYTIC ANAEMIA¹

By J. V. DACIE, P. L. MOLLISON,² NANCY RICHARDSON,³
J. G. SELWYN, AND L. SHAPIRO

(From the Department of Pathology, Postgraduate Medical School of London)

With Plates 10 and 11

THERE are three well-recognized varieties of haemolytic anaemia due to heritable abnormalities of the red cells, namely, hereditary spherocytosis (congenital acholuric jaundice), Mediterranean anaemia (Cooley's anaemia, thalassaemia), and sickle-cell anaemia. In addition there are less well recognized varieties which differ both clinically and pathologically from the well-known types. As yet only a few of these atypical cases have been described (see *Discussion*). In some the absence of spherocytosis has been emphasized as a characteristic feature; in others there has been an obvious disturbance in haemoglobin synthesis. Other cases seem to be related to familial elliptocytosis, or to be variants of hereditary spherocytosis. The purpose of the present paper is to describe the occurrence of atypical congenital haemolytic anaemia of several different types, to review the literature, and to discuss the mechanism of haemolysis and of inheritance.

Methods

Red-cell counts, leucocyte counts, platelet counts, reticulocyte counts, and packed-cell-volume (haematocrit) and haemoglobin estimations were carried out on venous blood by standard methods (Dacie, 1950). Mean red-cell diameters were calculated by Price-Jones's method from stained films. Osmotic fragility was estimated by a modification of the method of Parpart, Lorenz, Parpart, Gregg, and Chase (1947), and was in most cases also estimated after incubating defibrinated blood for 24 hours at 37° C. (Young, 1947; Varadi, 1951; Young, Izzo, and Platzer, 1951). The rate of spontaneous haemolysis (autohaemolysis at 37° C.) was studied with defibrinated blood. Two-millilitre volumes of blood collected under sterile conditions were delivered into a series of small sterile bottles of 5 ml. capacity, which were then placed in an incubator at 37° C. After having been left undisturbed for 24 or 48 hours, paired samples were centrifuged after gentle but thorough mixing, and the amount of liberated haemoglobin in the supernatant serum was compared, by means of a photoelectric colorimeter, with standards made by haemolysing whole blood in

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² Medical Research Council's Blood Transfusion Research Unit, Postgraduate Medical School of London.

³ Epsom District Hospital Group Laboratory.

N/150 ammonia. The amount of haemolysis was contrasted with that of a control normal blood incubated under the same conditions at the same time. Mechanical fragility was estimated with 2-ml. samples of patients' blood after adjustment of the packed cell volume to 45 per cent. Five glass beads of about 4 mm. diameter were added to the blood, which was then rotated in a 75×10 mm. tube at 33 r.p.m. for two hours. The haemoglobin liberated in the supernatant fluid was then estimated as a percentage of the total haemoglobin content of the sample with a photoelectric colorimeter. A control sample of normal blood was set up at the same time, and the amount of haemolysis of the patient's blood was contrasted with that of the normal sample. The survival of transfused red cells was estimated by a modification of the Ashby method of differential agglutination (Dacie and Mollison, 1943). In some cases powdered anti-M globulin was used, as described by Ebert and Emerson (1946). Tests for abnormal anti-red-cell antibodies were carried out as described by Dacie (1950). Spectrophotometric analyses and other physical studies of the haemoglobins of certain patients of the present series have been carried out by Drs. E. R. Holiday, G. H. Beaven, and J. C. White, and will be published separately.

Case Reports

Cases 1 to 5. Non-spherocytic congenital haemolytic anaemia

Case 1. M. C., a married woman aged 30 years. When aged two and a half years she underwent splenectomy for anaemia and jaundice, from which she is believed to have suffered since infancy. She made a good recovery from the operation, but was readmitted into hospital on several occasions during childhood on account of jaundice. However, she led a more or less normal life and attended school regularly. In June 1943 she was admitted into Hammersmith Hospital in a semi-comatose condition; she was extremely pale and moderately jaundiced. There was pyrexia (102° F.) and tachycardia; the jugular venous pressure was raised, and the liver was palpable. Her haemoglobin was as low as 1.5 gm. per 100 ml., and there were about 500,000 red cells per c.mm. She received transfusion, and recovered. Later in the year an exploratory laparotomy was undertaken. No splenunculi were found, but one of several dark glands in the mesentery was shown to be a hyperplastic lymph-gland. Since 1943 her blood count and clinical state have remained almost unaltered. She is usually slightly jaundiced, but has led a moderately active life. Her blood count usually shows about 2,000,000 red cells per c.mm., with 50 to 70 per cent. reticulocytes, and about 8 gm. of haemoglobin per 100 ml. Examination of blood films (Plate 10, Fig. 3) showed that the red cells were mostly rounded macrocytes varying little in size (mean cell-diameter 8.7 μ). A few irregularly crenated and contracted corpuscles were, however, constantly to be found even in well-spread films of freshly drawn blood. There was marked polychromasia, and nearly every cell contained 'Pappenheimer' bodies (Pappenheimer, Thompson, Parker, and Smith, 1945; McFadzean and Davis, 1947; Dacie and Doniach, Figs. 1, 2, and 8, 1947): in addition there were occasional Howell-Jolly bodies and scanty nucleated red cells. Red-cell osmotic fragility was slightly diminished, but it increased very markedly on incubation for 24 hours at 37° C. (Fig. 2). The rate of autohaemolysis was likewise strikingly increased. The direct Coombs and acid-serum tests were negative. Other haematological data are given in Tables I and II.

TABLE I
Haematological Data and Summaries of Clinical Histories

Case number	Sex	Age (years)	Red cells (millions/c.mm.)	Haemoglobin (gm./100 ml.)	Mean corpuscular volume (c. μ)	Reticulocytes (%)	White cells (per c.mm.)	Platelets (per c.mm.)	Serum bilirubin (mg./100 ml.)	Summary of clinical history
1	F	30	1.5-2.3	7-9	113-20	50-70	7,000-12,000	400,000-800,000	1.5-2.0	Splenectomy 27 years previously. Severe haemolysis still persists
2	M	7	2.4-2.8	8.4-9.6	114	14-28	Splenectomy 3 years previously. Haemolysis persists
3 ^a	M	17	1.7	7.0	102	4	8,000	800,000	..	Before splenectomy
3 ^b			2.3-2.4	11.0-11.3	126	9	1.6	1 year after splenectomy. Haemolysis persists
4	F	13	2.4-2.5	9.6-10.0	118-25	50-55	9,000	400,000	1.8	Splenectomy 7 years previously. Active haemolysis persists
5	M	14	3.4-3.5	11.0-11.5	96-102	4-6	3,000-6,000	140,000-250,000	3.3-5.0	Jaundiced, but leads a normal life. Spleen not palpable
6	M	22	5.0	17.5	90	5-11	5,000-6,000	..	2.2	Slightly jaundiced; leads normal life. Palpable spleen
7 ^a	F	28	3.2-3.4	10.8-12.1	91-103	12-17	5,000-6,000	170,000	1.4	Slightly jaundiced. Gall-stones. Palpable spleen
7 ^b			4.3	13.0	93	2	5,000	320,000	0.4	6 weeks after splenectomy and cholecystectomy.
8	M	33	4.2-5.2	14.7-18.8	90-110	3-9	5,000-6,000	..	0.5-1.4	In good health; occasional slight jaundice. Palpable spleen
9	M	31	5.0	15.2	92	3	6,000	..	0.5	In good health; no jaundice. Palpable spleen
10 ^a	M	19	2.8-3.7	11.1-13.5	101-23	1-5	9,000-10,000	320,000	1.8-2.8	Ulcerated legs; intermittent jaundice. Spleen palpable
10 ^b									1.2	2 years after splenectomy; still slightly jaundiced
11 ^a	M	.. ³	4.2	12.6	127	4	9,000	230,000	..	10 days after birth. Anaemic. Spleen palpable
11 ^b			7.0	13.6	.. ⁵⁶	3	27,000	2½ years after splenectomy; clinically well
12	F	6	2.0-2.5	6.0-9.6	72-92	10-26	14,000	Died nearly 2 years after splenectomy. Haemolysis persisted, associated with purpura and uremia (nephritis)
							7,000-28,000	10,000-270,000	0.9	

Further history. In 1948 she married; she has been pregnant twice. On the first occasion she was delivered of a macerated full-term foetus. The second pregnancy resulted in the birth, in April 1951, of a male infant who has so far appeared to be entirely healthy, and whose blood appears to be normal. M. C. has received transfusions on several occasions. The survival of transfused normal red cells has been studied three times, and on each occasion has appeared

TABLE II
Further Haematological Data and the Results of Transfusion Studies

Case number	Osmotic fragility	Change in osmotic fragility after incubation at 37° C. for 24 hrs.	Mechanical fragility	Autohaemolysis after incubation at 37° C. for 48 hrs.	Survival of transfused normal red cells
1 (after splenectomy)	Slightly diminished	Greatly increased	Normal	Very greatly increased (20 x normal control)	Normal, or possibly prolonged
2 (after splenectomy)	Diminished	Normal	Normal
3 (after splenectomy)	Greatly diminished	Increased; but less fragile than a normal control	Slightly increased (2 x normal control)	Normal	..
4 (after splenectomy)	Diminished	Greatly increased	Normal before incubation (2 x normal control after 24 hrs. at 37° C.)	Greatly increased (9 x normal control)	..
5	Normal	Increased; but fragility of some cells diminished	Normal	Normal	..
6	Normal	Increased; but not more than a normal control	Normal	Increased (4.5 x normal control)	Normal
7	Normal (upper limits)	Increased; slightly more than a normal control	Normal	Increased (4 x normal control)	..
8	Normal (upper limits)	Increased; slightly more than a normal control	Normal	Increased (4 x normal control)	..
9	Normal	Increased; but not more than a normal control	Normal	Normal	..
10a (before splenectomy)	Normal or slightly diminished	Normal	Normal
10b (after splenectomy)	Slightly diminished	Increased; but fragility of some cells diminished	Normal	Normal	..
11 (after splenectomy)	Much increased	Still further increased	Increased (2 x normal control)	Greatly increased (8 x normal control)	Normal
12 (after splenectomy)	Moderately increased	Impaired

to be normal or slightly prolonged. On the first occasion (1947) the estimates of the numbers of surviving red cells, when plotted against time, fell on a straight line which cut the time axis at a point 145 days after transfusion. On the second occasion the finding of a small residue of transfused cells 150 days after transfusion again suggested that normal red cells might be surviving for an abnormally long time in the patient's circulation. On the third occasion the patient was pregnant, and blood-volume changes interfered with the estimation of the mean life of the transfused red cells. The evidence from the first and second transfusion experiments suggests that in this patient transfused normal red cells survived for an abnormally long time, and this may have been related to the fact that she had undergone splenectomy. The sequence of events following the second series of transfusions is illustrated in Fig. 1. There was great temporary benefit; the plasma-bilirubin dropped to 0.5 mg. per 100 ml., and this

fall was associated with a marked diminution in the output of her own (abnormal) red cells, brought about, it is thought, by a reduction in the intensity of the 'anaemia stimulus'. Most of the transfusions were given during the two pregnancies, as it was thought desirable to try to maintain a haemoglobin level

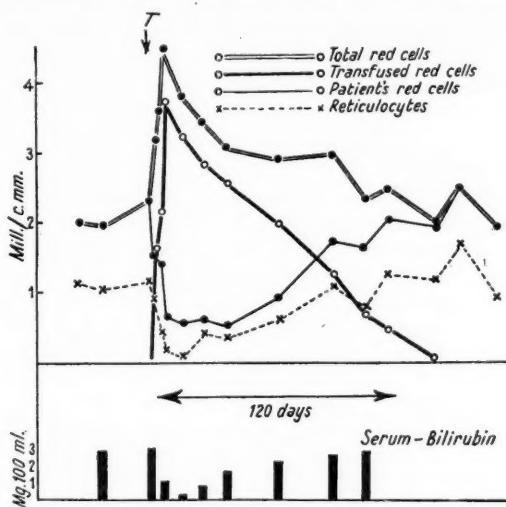


FIG. 1. Haematological changes after a large transfusion of blood (T).

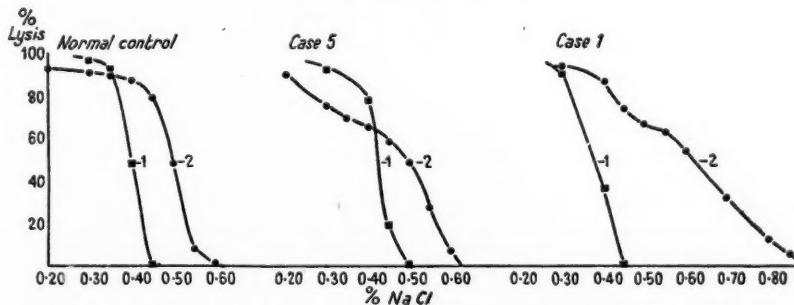


FIG. 2. The osmotic fragility of defibrinated blood before and after 24 hours' incubation at 37°C. in a normal control, Case 5, and Case 1. (1) Osmotic fragility before incubation; (2) osmotic fragility after incubation.

greater than 70 per cent. During the first pregnancy she was admitted into hospital with symptoms and signs of serum hepatitis, from which she made a good recovery. Target cells appeared in her circulation about one week after the onset of the illness; they increased in numbers until the end of the third week, and persisted for six or seven weeks. It was interesting to note that only the transfused normal corpuscles assumed the target form, and that this change did not affect their steady elimination from the circulation at the normal rate. Her own red cells, each marked by Pappenheimer bodies, were not altered; possibly their life in the circulation was too short for the change in shape to take place (Plate 10, Fig. 4).

Family history. Her father died of pneumonia at the age of 46 years; he had never suffered from anaemia or jaundice. Her mother is alive and well; her blood has been examined, and appears to be normal. Aunts and uncles likewise seem to have been free from the disease. M. C. was the second of three sisters. The eldest is alive and well; her blood is normal. The younger sister suffered from a haemolytic anaemia, and she, too, underwent splenectomy when she was two years of age. During childhood she was persistently jaundiced and anaemic and, like her elder sister, she developed a haemolytic crisis in 1943 when aged 18 years; she died of pulmonary oedema and myocardial failure.

Case 2.⁴ R. L., a boy aged seven years. He was noticed to be jaundiced during his first few days of life, but from then until 10 months old he appeared to be a normal healthy child. Since the age of 10 months he has been noticed to be slightly jaundiced. On occasions the jaundice has deepened and the child has become listless and febrile; the urine has become darker and the child has seemed to be paler. In April 1948 he was admitted to University College Hospital. Haemolytic anaemia was diagnosed and splenectomy performed on June 14. The spleen was $4\frac{1}{2}$ in. \times 3 in. in size, and of normal colour and consistency. The child was first investigated by us in October 1948, through the courtesy of Dr. R. E. Bonham-Carter, at a time when it was clear that haemolysis had not been influenced by removal of the spleen. There were 2,800,000 red blood-cells per c.mm., with 28 per cent. reticulocytes. The red cells were mostly round and slightly macrocytic, with little variation in size. There were very few poikilocytes, but there was marked polychromasia. Numerous small Pappenheimer bodies, occasional Howell-Jolly bodies, and a few target cells were seen. Osmotic fragility was found to be slightly diminished, and the direct Coombs and acid-serum tests were negative. He was re-examined in December 1949 and January 1950, and similar results were obtained. In 1949 the survival of transfused red cells was studied and found to be normal, approximately one-fourth of the transfused cells being present 96 days after transfusion. Other data are given in Tables I and II.

Family history. R. L.'s parents, and his sister aged 14 years, are alive and well. The only possibly abnormal finding in their blood is a tendency to have reticulocyte counts at the upper range of normal: in the mother's case 2·5 per cent. and 2·6 per cent. with 14·1 gm. haemoglobin per 100 ml. (two observations), in the sister's case 2·1 per cent. with 12·6 gm. haemoglobin per 100 ml., but in the father's case 1·2 per cent. (within the normal range). Blood films from all three were normal.

Case 3. O. F., a young man now aged 17 years. He was first found to be jaundiced and anaemic in 1938, at four years of age, when he was admitted into hospital for excision of a cyst (? thyroglossal) in the mid-line of the neck. Later in the same year an enlarged gland in the right side of his neck was aspirated and found to contain 'tuberculous pus'. In 1948 he was admitted into a surgical ward of the West Middlesex Hospital for treatment of undescended testicles. He was found to be severely anaemic, and received transfusions. He was investigated by us through the courtesy of Dr. J. A. Torrens. His red-cell count at this time (after transfusion) was about 1,700,000 per c.mm., with 7·0 gm. haemoglobin per 100 ml. and 4 per cent. reticulocytes. The red cells varied moderately in size, with some macrocytosis and a tendency to elliptocytosis. Occasional pear-shaped poikilocytes and small contracted corpuscles were present. After splenectomy (see below) there was increased macrocytosis and pronounced target-cell formation, and also an increased proportion of corpuscles which

⁴ This case has already been referred to briefly by Mollison (1951).

underwent irregular crenation. Pear-shaped poikilocytes were inconspicuous. Moderate polychromasia persisted, and there were numerous Pappenheimer bodies and occasional Howell-Jolly bodies. Red-cell osmotic fragility was diminished; the rate of autohaemolysis was normal. The Coombs and acid-serum tests were negative. Other data are given in Tables I and II. Splenectomy was done on December 29, 1948. His blood was examined on two subsequent occasions, one year and three years after splenectomy. On the last occasion there were about 2,400,000 red cells per c.mm., with 9 per cent. reticulocytes, and 11.3 gm. haemoglobin and 1.6 mg. bilirubin per 100 ml. The patient leads a moderately active life.

Family history. This is negative. The patient's father, mother, and two brothers are alive and well. The mother's blood is normal; the others have not been examined. There is no history of anaemia or jaundice in any other relative.

Case 4. J. M., a girl aged 13 years. She was a first child, and she weighed 4½ lb. at birth. As an infant she was noticed to be pale, and when she was 18 months old a diagnosis of splenic anaemia was made. From the age of two years onwards she suffered from recurrent attacks of mild jaundice. When she was six and a half years old splenectomy was performed; she received transfusion and left hospital in good condition. Two years later she was found to be anaemic, and was given a transfusion again. She was first seen by us through the courtesy of Dr. W. P. H. Sheldon in November 1951, seven years after splenectomy. She was then moderately anaemic and slightly jaundiced. There were no other abnormal physical signs, but she was noticed to be small for her age; her height was 4 ft. 10 in. and her weight 5 stone 4 lb. There were about 2,500,000 red blood-cells per c.mm., and 10 gm. haemoglobin per 100 ml. She appeared to be maintaining a stable haemoglobin level, and had about 50 per cent. reticulocytes. The red cells were mostly rounded macrocytes with little variation in size, but there were occasional irregularly crenated and contracted cells. Polychromasia was marked, and there were numerous small Pappenheimer bodies and occasional Howell-Jolly bodies. Red-cell osmotic fragility was slightly diminished, but increased strikingly on incubation for 24 hours, and the rate of autohaemolysis was greatly accelerated. The Coombs and acid-serum tests were negative. Other data are given in Tables I and II.

Family History. Her mother and father and a younger sister are alive and well. A third full-term baby died soon after birth. The blood counts of the father and sister are normal. The mother's blood has been tested on one occasion; there were 4,200,000 red cells per c.mm., with 6 per cent. reticulocytes,⁵ the haemoglobin was 12.9 gm. per 100 ml., and the serum-bilirubin 0.25 mg. per 100 ml. The red-cell morphology was normal, as were the osmotic fragilities before and after incubation and the rate of autohaemolysis. The raised reticulocyte count is unexplained, and it seems possible that the mother has a mild form of the anaemia from which her daughter is suffering.

Comment (Cases 1 to 4). These patients belong to a fairly homogeneous group; their disorder may conveniently be described as non-spherocytic congenital haemolytic anaemia. All four patients underwent splenectomy, but none benefited from it, haemolysis *in vivo* remaining moderately to greatly increased. They all had a macrocytic anaemia with evidence of active regeneration. Poikilocytes were inconspicuous, but crenated and irregularly contracted corpuscles were not infrequent in Cases 1, 3, and 4. Pappenheimer bodies were abundant,

⁵ Three months later there were 4,100,000 red cells per c.mm., with 5 per cent. reticulocytes and 12.0 gm. haemoglobin per 100 ml.

and particularly conspicuous in the cells of Case 1. In all four patients (after splenectomy) red-cell osmotic fragility was diminished. In two patients (Cases 1 and 4) incubation at 37° C. for 24 hours resulted in a great increase in fragility, with slight haemolysis in 0·85 per cent. saline. The mechanical fragilities were normal, or slightly increased (particularly after 24 hours at 37° C.). In two patients (Cases 1 and 4) there was a great increase in the rate of spontaneous haemolysis on incubation for 24 and 48 hours; in Cases 2 and 3 the results did not seem to be abnormal.

Case 5. G. S., a boy aged 15 years. He was jaundiced for a few days after birth. Jaundice was again noticed when he was five years of age, and was possibly present later from time to time. When he was 10 years of age he became strikingly jaundiced, and was kept in bed for one month. Within two months jaundice reappeared, and since then it has never cleared completely. His general condition has remained good throughout. His stools are normal, and urobilin, but not bilirubin, has been detected in the urine. He is of normal intelligence, height, and weight, and leads a normal life. Except for jaundice there are no abnormal physical signs; his spleen cannot be felt, and his liver appears normal on palpation. The patient was referred to us by Dr. M. Dynski-Klein in July 1950. Since then his blood has been examined by us on six occasions; the average red-cell count has been about 3,500,000 cells per c.mm., with about 5 per cent. reticulocytes, and plasma-bilirubin 4 mg. per 100 ml. The red cells varied slightly in size, and there were occasional macrocytes. There was a slight tendency to elliptocytosis and slight polychromasia. Red-cell osmotic fragility was normal, and the Coombs and acid-serum tests were negative. Other data are given in Tables I and II.

Family history. This is negative. His father and mother and a younger sister are well. However, his mother was found to be slightly anaemic; her haemoglobin was 12 gm. per 100 ml., red cells 3,500,000 per c.mm. with 2·5 per cent. reticulocytes, and packed cell volume 37 per cent. Many of her red cells were slightly oval in shape, and the general appearance of her blood film was similar to that of her son. Moreover her plasma-bilirubin was 0·9 mg. per 100 ml., and it seems possible that she is suffering from a mild degree of the same disorder as her son. G. S.'s sister's blood was normal; his father's blood has not been examined.

Comment. This boy is less anaemic than are the preceding four patients; presumably his rate of haemolysis is less, although his serum-bilirubin concentration is relatively high. His spleen has not been removed, and it is not clear whether he should be classified with the preceding group. His cells behaved differently on incubation *in vitro*; in contrast to the findings in Cases 1 and 4, incubation of his blood for 24 hours resulted in a diminution in fragility of part of the red-cell population (Fig. 2). The rate of autohaemolysis was not increased during 48 hours' incubation.

Cases 6 to 9. ? Variants of hereditary spherocytosis

Case 6. J. H., aged 22 years. He was first noticed to be jaundiced for two weeks when 10 years of age. Three years later, in 1941, he again became jaundiced. His urine was dark and his stools were pale for three or four weeks; the jaundice is said to have persisted for at least three months. In 1948 he was jaundiced again, and in May 1950 he was in hospital for as long as four months. He was

first seen by us in November 1950. He was then found to be an intelligent young man of normal height and weight. Except for slight clinical jaundice and a just-palpable spleen there were no abnormal physical signs. Blood examination revealed no anaemia, although there was a persistent reticulocytosis of 5 per cent. to 11 per cent. The red cells were rounded normocytes with a slight tendency to microspherocytosis (mean cell-diameter 7.0μ). Polychromasia was slight. His red-cell osmotic fragility was at the upper edge of the normal range; on incubation at $37^\circ C.$ the changes were not different from those observed in control samples of normal blood; the Coombs and acid-serum tests were negative. Transfusion experiments were performed: first, 400 ml. of blood were taken from the patient and transfused into a suitable recipient. The survival of the red cells was strikingly less than that of normal red cells transfused at the same time, and it was calculated that the red cells of J. H. had a mean life of only 12 or 13 days. Secondly, the patient himself received a transfusion of normal corpuscles; their survival was strictly normal. Other data are given in Tables I and II.

Family history. This is negative. His mother, father, and two brothers are alive and well. Blood films of his father and mother were normal, as were their red-cell osmotic fragilities before and after incubation for 24 hours at $37^\circ C.$

Comment. Although the family history seems to be negative, it is possible that this man is suffering from a mild form of 'typical' hereditary spherocytosis. Microspherocytosis of the red cells was just appreciable. The red-cell osmotic fragility was normal or at the upper limits of normal.

Case 7. Q. G., a married woman aged 28 years. As a child she frequently complained of abdominal pain and biliousness, and chronic appendicitis was diagnosed. In 1944 she married, and soon afterwards was operated on for acute appendicitis; this event was followed by a miscarriage. The following year she again became pregnant, and after delivery she was noticed to be anaemic. She had a second normal pregnancy in 1947. In 1948 she suffered from severe abdominal pain and became deeply jaundiced. Gall-stones were diagnosed, and her spleen was also found to be palpable. She was first investigated by us in September 1951. Physical examination showed a well-developed young woman; a slight tinge of jaundice and a palpable spleen were the only abnormal physical signs. Radio-opaque gall-stones were revealed by cholecystography. Blood examinations revealed a moderate anaemia and slight jaundice; there were 3,300,000 red cells per c.mm., with 12 to 16 per cent. reticulocytes, and bilirubin $1.4\text{ mg. per }100\text{ ml.}$ The red cells were normocytes, varying moderately in size with a tendency to an oval shape (mean cell-diameter 7.0μ) (Plate 10, Fig. 6). There was possibly slight microspherocytosis. Polychromasia was slight. Red-cell osmotic fragility was at the upper limits of normal. Other data are given in Tables I and II. Cholecystectomy and splenectomy were carried out on September 28, 1951, by Mr. R. H. Franklin. The spleen weighed 550 gm.; sections showed congestion with red cells, the appearance being indistinguishable from that seen in cases of 'typical' hereditary spherocytosis. Clinical recovery was uneventful, and jaundice completely disappeared. The blood count improved slowly; five weeks after operation the red-cell count had risen to 4,300,000 cells per c.mm., and the haemoglobin to $13.0\text{ gm. per }100\text{ ml.}$; there were 2.2 per cent. reticulocytes. The plasma-bilirubin was $0.4\text{ mg. per }100\text{ ml.}$

Family history. The patient's father is known to have been jaundiced all his life; he died aged 56 years of a mesenteric thrombosis soon after splenectomy. His red cells are said not to have been spherocytic, and their osmotic fragility to have been only slightly increased. Four of the patient's paternal aunts and

one paternal uncle had not suffered from jaundice, and the patient's mother is alive and well. She has two brothers, both affected to a slighter degree (Cases 8 and 9 of this series). A younger sister is apparently quite normal. Both Q. G.'s children, girls aged six and four years respectively, are apparently developing normally.

Case 8. N. G., a man aged 33 years, the elder brother of Case 7. He has had mild intermittent jaundice for many years, but this has not affected his general health. His spleen is just palpable, but he is not anaemic. His red-cell count has ranged from about 4,200,000 to 5,200,000 cells per c.mm., and haemoglobin from 14.7 to 18.8 gm. per 100 ml. The reticulocyte count has varied between 3 and 9 per cent., and the plasma-bilirubin has been as high as 1.4 mg. per 100 ml. The red cells were normocytes only varying slightly in size (mean cell-diameter 6.8 μ) (Plate 10, Fig. 5); there were a few poikilocytes, and there was slight microspherocytosis and polychromasia. Red-cell osmotic fragility was at the upper limit of the normal range. Autohaemolysis at 37° C. was accelerated. Other data are given in Tables I and II. He has a son aged four and a half months whose spleen is palpable. This infant, like his father, is not anaemic. The haemoglobin content of his blood was 13.8 gm. per 100 ml., with 3.6 per cent. of reticulocytes.

Case 9. I. G., a man aged 31 years, younger brother of Cases 7 and 8. He is affected even more mildly than his elder brother, and he has no symptoms referable to haemolytic anaemia. He has been neither anaemic nor jaundiced, though his spleen is just palpable. His red-cell count showed about 5,000,000 cells per c.mm., with 15.2 gm. haemoglobin per 100 ml. and 3 per cent. reticulocytes. The red cells were normal in size and shape. Plasma-bilirubin was 0.5 mg. per 100 ml. and red-cell osmotic fragility normal. The rate of autohaemolysis was not increased. I. G. has two small children, one of whom has a palpable spleen. They are not clinically anaemic or jaundiced. Their blood has not been examined.

Comment (Cases 7 to 9). These three patients are members of the same family. Case 7 was the most severely affected. She was moderately anaemic; her red cells tended to be oval in shape, and there was possibly slight microspherocytosis. The blood of Case 8 showed definite but slight microspherocytosis; that of Case 9 was hardly distinguishable from normal. In all three the osmotic fragilities were normal (at the upper limits of normality in Cases 7 and 8). Incubation of the blood of Cases 7 and 8 for 24 hours at 37° C. produced increases in fragility slightly greater than that of controls; the change produced in the blood of Case 9 (clinically only slightly affected) was identical with that of the control. Mechanical fragilities were normal initially; in Case 8, after 24 hours at 37° C., there was a definite increase compared with the control. The rate of autohaemolysis of the blood of Cases 7 and 8 was substantially increased; that of Case 9 was normal. These cases, like Case 6, may be slight variants of 'typical' spherocytic congenital haemolytic anaemia.

Case 10. A further type of congenital haemolytic anaemia, with marked macrocytosis and leg ulcers

Case 10. P. B., a young man aged 19 years. Until the age of 15 years he had been quite well, and considered himself to be normal in every way. Jaundice was the first abnormal sign, and has persisted on and off until the present time; it has never been great. In 1947, at the age of 16 years, ulcers developed on his

shins while he was serving in the Merchant Navy, and have never completely healed. In 1949 he was investigated at the London School of Tropical Medicine, but no satisfactory cause was found for the ulceration. In August of that year he was transferred to us by the late Professor F. Murgatroyd as a probable case of haemolytic anaemia. He was found to be a rather thin young man of average height and intelligence. Jaundice was just appreciable, and his spleen was easily palpable four inches below the costal margin. Areas of pigmentation, and small unhealed and partially healed ulcers, were present on the anterior surfaces of both shins. There were no other abnormal physical signs. Blood examination showed that he had a macrocytic anaemia, with about 3,000,000 red cells per c.mm., 11.4 gm. haemoglobin per 100 ml., and 3 to 5 per cent. reticulocytes. At this time many large macrocytes, round to slightly oval in shape, were present; in addition there were numerous microcytes, mostly oval or pyriform in shape, as well as some extremely small irregularly shaped fragments of cells. There was slight polychromasia, and occasional cells showed conspicuous diffuse punctate basophilic. After splenectomy (see below) the macrocytosis was more marked, and target cells were conspicuous (mean cell-diameter 9.3 μ) (Plate 11, Fig. 7). Irregularly contracted microcytes were more frequent, and many cells contained Pappenheimer bodies.

The sternal bone-marrow was hyperplastic, with increased erythropoiesis of normoblastic type. Plurinucleated erythroblasts, resulting from abnormal cell divisions, were unusually abundant, and a small proportion of the erythroblasts contained granules in their cytoplasm giving a positive test for inorganic iron (siderotic granules). Red-cell osmotic fragility was normal, and the average plasma-bilirubin was 2.5 mg. per 100 ml. Other data are given in Tables I and II. He was given a transfusion of normal blood; red-cell survival was normal, 83 per cent. of the normal cells being present 28 days after transfusion. Splenectomy was carried out on November 30, 1949, by Mr. R. H. Franklin. The spleen weighed 430 gm. Microscopically the splenic sinuses were filled with blood, and were unusually well defined. The pulp cords between the sinuses were compressed; the reticulin fibres were thickened, with some laying down of collagen. Erythrophagocytosis was not easily seen, nor was there much iron pigment. The patient made a good recovery from the operation, but there was little immediate alteration in his blood count, although the plasma-bilirubin level fell to less than 1 mg. per 100 ml. Two years after splenectomy the plasma-bilirubin was 1.2 mg. per 100 ml., and he was still anaemic, with haemoglobin 12.6 gm. per 100 ml. and red cells 2,800,000 per c.mm. The ulcers on his shins healed after splenectomy, but subsequently recurred; otherwise he has felt well, and considers himself free from jaundice.

Family history. His father and mother are alive and well. He has two brothers, one of whom had an attack of jaundice lasting six weeks three years ago. The other brother and two sisters give no history suggestive of anaemia and jaundice; nor have any other relatives apparently been affected. The blood of his mother, his two sisters, and a nephew have been examined. His mother (a blood donor) and his elder sister (pregnant) were found to be slightly anaemic—haemoglobin 12.2 gm. and 11.8 gm. per 100 ml. respectively. The morphology of their red cells was not significantly abnormal. The osmotic fragilities before and after incubation, and the rates of autohaemolysis, were also normal. The reticulocytes of all four were within the normal range. Thus no definite evidence of a haemolytic process was established in these relatives.

Comment. P. B.'s clinical history, the splenomegaly, and the ulcers on his legs were suggestive of 'typical' hereditary spherocytosis; but the blood picture,

with macrocytosis and extreme variation in red-cell size and shape, was quite distinct from the typical disease and from that of all the other patients of the present series. Osmotic fragility was normal; after splenectomy resistance was increased. The rate of autohaemolysis appeared to be normal both before and after splenectomy. Removal of the spleen did not seem to be of any real benefit; anaemia was not relieved, nor did jaundice altogether disappear.

Case 11. ? A variant of familial elliptocytosis

Case 11. D. H., aged three years. This boy was admitted into hospital when only 10 days old because of increasing pallor. He had been born at term, weighing $5\frac{1}{4}$ lb., after a normal labour. He was a pale but vigorous infant, not clinically jaundiced. The liver and spleen were palpable, but there were no other abnormal physical signs. There were about 4,200,000 red cells per c.mm., 7.4 gm. haemoglobin per 100 ml., and 3 per cent. reticulocytes in his peripheral blood. Examination of blood films revealed a striking variation in red-cell size, and numerous extremely small spherocytic microcytes. Moderate polychromasia and some nucleated red cells were present. During the three days following his first admission to hospital the haemoglobin level dropped to 3.6 gm. per 100 ml., and transfusion was given. Red-cell osmotic fragility after transfusion was found to be increased: there was 20 per cent. haemolysis in 0.50 per cent. sodium chloride, and the rate of autohaemolysis was accelerated. The child received five transfusions in the next six months, with considerable but only temporary benefit. The peripheral blood film indicated that most of the circulating cells were normal transfused cells, and this fact was confirmed by a study of cell-survival: six weeks after the fourth transfusion 60 per cent. of the transfused cells were still circulating. Apart from anaemia the general condition of the infant was good. He never became jaundiced, but the spleen became larger and was easily palpable. Splenectomy was successfully carried out by Mr. D. O. Davies on July 21, 1949, when the child was six months old, a transfusion being given before operation. Recovery was uneventful. The spleen weighed 55 gm.; sections revealed a moderate degree of congestion with red cells in the pulp, and relatively empty sinuses. The spleen pulp also contained much free iron. Immediately after the operation the red-cell count began to rise, and very small microcytes, often of irregular shape, appeared in the blood films. Two months after operation the majority of the red cells were obviously those of the patient; their osmotic and mechanical fragilities and rate of autohaemolysis were greatly increased. Other data are given in Tables I and II. The child has had no transfusion since splenectomy. The red-cell count, two and a half years after operation, has reached 7,000,000 cells per c.mm., with 13.6 gm. haemoglobin per 100 ml. The red cells are still strikingly abnormal in appearance (Plate 11, Fig. 8).

Family history. D. H. is the third of three sons. The first child died at the age of seven weeks of 'anaemia'. No pathological investigations were carried out. The second child, now aged five years, is clinically normal, but his red cells are moderately elliptic in shape. D. H.'s father and mother are both clinically normal, and not anaemic. The father's blood film appears normal; the mother's blood shows about the same degree of elliptocytosis as that of her second son (Plate 11, Fig. 9).

Comment. This infant seems to be suffering from a congenital haemolytic anaemia related to familial elliptocytosis. There is a positive family history: a sibling died of anaemia in infancy, and the blood films of an elder brother and

his mother show elliptocytosis. After splenectomy numerous fragments of red cells were persistently present in addition to microspherocytes, a picture quite unlike that of typical spherocytic congenital haemolytic anaemia. Osmotic fragility was increased, and this increase persisted after splenectomy. The operation resulted in marked clinical improvement.

Case 12. A further type with 'triangular' red cells

Case 12. V. G. was a girl aged six years. She was jaundiced at birth; jaundice persisted intermittently, and was associated with mild pallor. She kept fairly well, and developed normally, until she was four years of age. She then began to have haematuria associated with generalized petechiae and bruising. She required transfusion, and her spleen was removed in February 1949, with no effect on the course of the disease. Hypertension was discovered in August 1949, and from then on her urine contained protein, red cells, leucocytes, and casts. She was first investigated by us in December 1949, through the courtesy of Dr. R. E. Bonham-Carter. It was evident that she was suffering from a haemolytic anaemia complicated by a haemorrhagic diathesis and nephritis. Her clinical state fluctuated, but slowly deteriorated. Purpura and spontaneous bruising occurred intermittently, and she was repeatedly readmitted into hospital for transfusion. Her blood-pressure and blood-urea rose slowly, and on occasions she had gross haematuria. She gradually became stuporous, and died on December 28, 1950.

The blood findings are summarized in Tables I and II. Severe anaemia was prevented by transfusions; her red-cell count did not fall below about 2,000,000 per c.mm., nor her haemoglobin below 6.0 gm. per 100 ml. The reticulocyte count varied between 10 and 26 per cent. The platelet count was generally well below 100,000 per c.mm. Stained blood films presented a striking picture; most characteristic were large numbers of contracted and distorted microcytes with angular outlines, many being almost triangular in shape (Plate 11, Fig. 10). All stages between these cells and rounded normocytes were present. In addition normally shaped macrocytes showing diffuse basophilia were conspicuous. Pappenheimer bodies were present in some of the cells, and there were occasional Howell-Jolly bodies. When preparations of blood were incubated there was a tendency for the distorted corpuscles to become still more distorted, especially in the presence of reducing substances, and to become weakly birefringent, but no true sickling took place. Osmotic fragility was moderately increased. Other data are given in Tables I and II. A study of the survival of blood transfused to her in December 1949 showed that the transfused normal red cells were disappearing at an accelerated rate; elimination was complete in about 50 days. This was an unexpected finding, perhaps partly explained by chronic bleeding into the tissues, and possibly also by the effects of early uraemia; her blood-urea at the time was 55 mg. per 100 ml. There was no evidence of the presence of immune iso-antibodies which might have developed as the result of previous transfusions. A post-mortem examination was made three hours after her death. The most important findings were cerebral softening apparently due to a thrombus in the right middle cerebral artery, nephritis, congestion of the lungs, and hyperplastic, predominantly erythropoietic bone-marrow. Megakaryocytes were present in the marrow in normal numbers.

Family history. V. G. was the third of four children. The first child was jaundiced at birth; at seven months pallor and purpura developed, and at the age of two years the child died of haemorrhage, after attempts had been made to extract a bead from her nose. The second child was jaundiced at birth, and

died on the fourth day of life as a result of bleeding from the bowel. The youngest child is apparently healthy, but has not been examined. V. G.'s parents are alive and well. Her father has 14.8 gm. haemoglobin per 100 ml., with 0.2 per cent. reticulocytes and a normal blood film. The mother has 13.8 gm. haemoglobin per 100 ml., with 2.1 per cent. reticulocytes; on another occasion there were 3.1 per cent. reticulocytes. Her blood film appears normal.

Comment. This patient seems to have suffered from yet another type of hereditary blood dyscrasia, at least one, and possibly two, siblings having been affected. After splenectomy, which did not affect the clinical course of the disease, marked variation in red-cell size and shape was an invariable finding, densely staining microcytic and almost triangular-shaped poikilocytes being a characteristic feature. Osmotic fragility was moderately increased. Tests for sickling were negative.

Discussion

Red-cell morphology in atypical congenital haemolytic anaemias. The morphology of the red cells of the patients we have described is remarkable for its diversity; almost all the recognized deviations from the normal may be found in their blood films, as well as deviations not commonly met with. Certain of these changes will be described. Irregularly crenated and contracted red cells were conspicuous in films made from those patients who had undergone splenectomy; they were far less noticeable in the films of the patients who still possessed their spleen. The constant presence of these red cells seems to be an unexplained effect of splenectomy, for similar cells are frequently found in the films of patients who have had the spleen removed for other causes. The contracted and irregularly shaped microcytes present in large numbers in the blood of Cases 11 and 12 appear to be schizocytes—products of red-cell fragmentation. In Case 11 they seemed to be rapidly removed from the blood-stream by the spleen, for they appeared in large numbers only after splenectomy. It is interesting to notice that in Cases 11 and 12 the red-cell osmotic fragility was increased, illustrating the fact that it is not only rounded microspherocytes which are osmotically fragile. Very occasional red cells in the films of Cases 6 and 7 showed a peculiar appearance, as if part of their substance had been indented and pulled outwards by a pair of pincers (Plate 10, Fig. 6). 'Pincerred' cells of similar appearance were illustrated by Rous and Robertson (1917) in rabbits' blood, and were considered to be fragmenting cells, present in small numbers in normal rabbit blood and in larger numbers in blood from the spleen. We have also found 'pincerred' cells in small numbers in the blood films of cases of apparently 'typical' hereditary spherocytosis; their presence is therefore not characteristic of any single type of haemolytic anaemia. 'Pappenheimer' bodies (Plate 10, Fig. 3) could be found in well-stained films in many of the red cells of those patients who had undergone splenectomy. Their significance is still uncertain; they may be found in typical hereditary spherocytosis as well as in atypical types, and also in acquired haemolytic anaemia and other blood dyscrasias. Target cells (Barrett, 1938) could be found in small numbers in the

peripheral blood of Cases 1, 2, 4, and 12. They were present in large numbers in the films of Case 10, and were very conspicuous in Case 4; all these patients had had their spleens removed. As already mentioned, in Case 1 transfused red cells temporarily assumed a target shape during an attack of serum hepatitis. It is clear that the presence of target cells in the blood of a patient with congenital haemolytic anaemia does not necessarily indicate a diagnosis of Mediterranean anaemia.

Cases in the literature. Atypical cases of congenital haemolytic anaemia, described under various titles, may be found in the literature. It seems that, like our own cases, most of them can be classified into several fairly definite groups such as non-spherocytic congenital haemolytic anaemia, hypochromic congenital haemolytic anaemia, haemolytic anaemia with elliptocytosis, and variants of hereditary spherocytosis.

(1) *Non-spherocytic congenital haemolytic anaemia.* Haden (1947) described the incidence in two families of 'haemolytic jaundice without spherocytosis'. Anaemia was of the macrocytic variety; red-cell osmotic fragilities were normal, and splenectomy in one case did not alter the course of the disease. At least three members of two generations of the first family (American) and four members of three generations of the second family (of Hungarian origin) were affected, but it is likely that the disease was not the same in each. In the first family spontaneous haemolysis of the blood *in vitro* was noted in two of the three cases; in the second family punctate basophilia was conspicuous. Crosby (1950) described in detail an American family, of mixed English and French origin, in which a relatively mild chronic haemolytic anaemia was found in seven (possibly in nine) out of 36 members. Brachyphalangia was also found, but this was not necessarily associated with the anaemia. The propositus was subjected to splenectomy, but without significant improvement. His red cells were biconcave disks, with occasional oval and 'tear-drop' forms and rare spherocytes. Osmotic fragility was slightly diminished. After splenectomy up to 45 per cent. of siderocytes appeared in the peripheral blood, and there was an increase in mean cell-diameter. Mechanical fragility was normal, but Crosby demonstrated an increased tendency to haemolysis on incubation. When transfused to a normal recipient the patient's cells survived for only 12 days; normal red cells transfused to the recipient survived well. Porphobilinogen was demonstrated in his urine on several occasions. Kaplan and Zuelzer (1950) reported the incidence of haemolytic anaemia in three out of six children of French-Canadian extraction belonging to one family. Each child suffered from a moderately severe normocytic anaemia; about half the corpuscles were slightly to moderately oval in form. There were no target cells or spherocytes, and osmotic and mechanical fragilities were normal. There was a tendency towards the development of a mongoloid facies. The results of cross-transfusion experiments were similar to those in 'typical' congenital haemolytic anaemia; that is to say, normal red cells survived normally in the patient's circulation (two cases), and red cells from the patient transfused to a normal recipient survived for a shorter time than normal (one case). Cases 1 to 4 of our own series are clearly somewhat

similar to the patients described by Haden (1947), Crosby (1950), and Kaplan and Zuelzer (1950).

A rather different type of congenital haemolytic anaemia in a Negro was described by Feinberg and Watson (1951). The patient was one of eight children, the others being apparently unaffected. The most characteristic feature of his anaemia was the large number (10·8 per cent.) of stippled red cells; osmotic and mechanical fragilities were normal, and tests for sickling negative. An interesting example of yet another variant of congenital haemolytic anaemia is the case of Aldrich, Hawkinson, Grinstein, and Watson (1951). Their patient, a little girl, presented the symptoms of congenital porphyria as well as of haemolytic anaemia. She had a slightly macrocytic anaemia, with 'curious' granulation in some of the red cells and possibly some spherocytes. Osmotic fragility was normal. Splenectomy resulted in a marked improvement; there was a diminution in the anaemia, as well as in the excretion of porphyrins and in skin sensitivity to light.

(2) *Atypical hypochromic congenital haemolytic anaemias.* Another group of congenital haemolytic anaemias appears to be associated with disturbances of haemoglobin synthesis, or with heritable abnormalities of the haemoglobin molecule. It is doubtful whether these are the only abnormalities; in some cases erythropoiesis may also be defective owing to other causes. The net result, however, is that the abnormal cells have an impaired viability in the peripheral circulation, and that the anaemia is to some extent haemolytic. Mediterranean anaemia is a well-known type belonging to this group, but there appear to be other somewhat similar, yet distinct, disorders which affect people not of Mediterranean stock (Cooley, 1945; Rundles and Falls, 1946; Mills and Lucia, 1949; Mills, Huff, Krupp, and Garcia, 1950). As in Mediterranean anaemia, there is in this latter group microcytosis, and there are signs of faulty haemoglobin formation; in some cases siderocytes and erythroblasts containing inorganic iron have been conspicuous (Mills and Lucia, 1949; Estren and Dameshek, 1949; Mills, Huff, Krupp, and Garcia, 1950). Oval red cells are frequently found in films of peripheral blood; in some of the patients of Rundles and Falls elliptocytosis without anaemia appeared to indicate a carrier state. In general, the picture the patients present is a severe hypochromic anaemia refractory to treatment with iron, rather than a haemolytic anaemia. None of the patients of the present series appears to belong to the above group. In P. B. (Case 10) the situation seems to be analogous in so far as there is very marked morphological evidence of dyshaemopoiesis; but there is relatively little evidence of a disturbance of haemoglobin synthesis. Although the red cells vary markedly in haemoglobin content, they are macrocytic, and the mean cell-haemoglobin concentration (31 to 34 per cent.) is normal. A few erythroblasts in the marrow contain stainable iron-containing granules; other cells show mitotic abnormalities. Fanconi's (1939) case of hyperchromic elliptical-cell haemolytic anaemia seems to have certain features in common with our case, including the ineffectiveness of splenectomy. Other interesting cases difficult to classify are those reported by Introzzi (1935) and Debler (1939-40), and the type of possibly

racially-determined haemolytic anaemia described in Filipinos by Stransky and Regala (1946) and Stransky (1951), whose patients suffered from a microcytic or normocytic hypochromic anaemia (macrocytic after splenectomy) with erythroblastæmia and normal osmotic fragility. The authors believed this type of anaemia to be distinct from Mediterranean anaemia. Splenectomy had no beneficial effect. Recently a new heritable abnormality of haemoglobin, 'haemoglobin III', has been described by Kaplan, Zuelzer, and Neel (1951). Haemoglobin III, found so far in American Negroes, can be distinguished from normal and sickle-cell haemoglobin by electrophoretic analysis. When combined with sickle-cell haemoglobin its presence is associated with a mild haemolytic anaemia; when combined with normal haemoglobin its presence is indicated by a high incidence of target cells, but no anaemia.

(3) *Elliptocytic congenital haemolytic anaemia.* There is some controversy in the literature as to the frequency with which haemolytic anaemia is found in association with familial elliptocytosis (elliptical-cell trait, 'ovalocytosis'). Wyandt, Bancroft, and Winship (1941) and Hedenstedt (1947), in reviews, concluded that there is no direct relationship between elliptocytosis and anaemia. On the other hand, there are now enough reports in the literature to suggest that, while in most instances there seems to be no evidence of an increased rate of haemolysis, in exceptional cases haemolytic anaemia may develop (Grzegorzevski, 1933; Lambrecht, 1938; Mason, 1938; Griffin and Watkins, 1939; Wyandt, Bancroft, and Winship, 1941; Penfold and Lipscomb, 1943; Holst-Larsen, 1947; Guasch and Raichs, 1948; Lendval, 1949). The reports of Mason (1938), Wyandt, Bancroft, and Winship (1941), and Holst-Larsen (1947) are most significant. Mason's Case 1, a boy aged 13, suffered from a haemolytic anaemia severe enough to warrant transfusion. His mother's red cells were typically elliptic, but she was not anaemic; his father's blood was normal, but three children of the father's sister died of anaemia of an unknown type. The genetic background of the single case of anaemia described by Wyandt, Bancroft, and Winship was also remarkable; the red cells of both parents were typically elliptic, and the small spherocytic and elliptic cells of their anaemic son may thus represent the elliptic trait in a homozygous state. Holst-Larsen's cases were remarkable for the variable intensity of the cellular abnormality; at least seven patients out of 11 were anaemic, with raised reticulocyte counts and increased osmotic fragility. Unmistakable haemolytic anaemia was present in three branches of a single family, the elliptic red cells being admixed with small microspherocytes and irregularly shaped microcytes in the more anaemic patients. The photomicrograph of the blood of his Case 11 is very similar to that of D. H. (our Case 11). Holst-Larsen's cases may illustrate the variability of the penetrance of the gene for elliptocytosis and the resultant effect on the red blood-cells.

(4) *Atypical hereditary spherocytosis.* Especially since the paper of Gänsslen, Zipperlen, and Schüz (1925) it has been recognized that hereditary spherocytosis may exist in all grades of severity, and in forms in which one or more of the characteristic features may be missing; in some cases there may be no anaemia,

in others no jaundice; the spleen may be impalpable in some, and in others—in 10 per cent. of cases according to Gänsslen and his fellow-workers—osmotic fragility may be normal. Gänsslen, Zipperlen, and Schüz also emphasized the fact that very mild forms existed, in which the trait could only be recognized by repeated observations and by appreciation of slight deviations from the normal. Case 6 of the present series may be such a case; the patient suffered from jaundice and hyperbilirubinaemia, but he was not anaemic, nor was red-cell osmotic fragility increased, although there was a suspicion of microspherocytosis. Cases 7, 8, and 9 seem to be suffering from a disorder slightly different from hereditary spherocytosis, and not to be merely mild examples of that disease. Case 8 was the first member of the family to be examined; he was not anaemic, and had a normal osmotic fragility; but his spleen was palpable, he was intermittently jaundiced, and there was a suggestion of slight microspherocytosis in films of his blood. His sister (Case 7) was next examined. She was anaemic, and it was clear that haemolysis was proceeding quite rapidly. Microspherocytosis was no more marked than in her brother, and osmotic fragility was normal. On the other hand, her red cells were definitely more oval than normal.

Mechanism of haemolysis in atypical congenital haemolytic anaemia. Although the morphological abnormality of the patients' red cells and their behaviour *in vivo* appear to differ from case to case, the effect in all is a greater or lesser diminution of their life-span *in vivo*. It is not known how this diminution is brought about, though presumably it is due to an intrinsic defect of the red-cell structure or metabolism. In some cases the diminution in life-span appears to be independent of the action of the spleen. Cases 1 to 4 of this series may be of this type; in two of them at least there was an increased rate of spontaneous haemolysis *in vitro*, and splenectomy proved to be of no benefit. In other cases the red-cell abnormality seems rather to resemble that of typical hereditary spherocytosis. That of Case 11, and possibly that of Case 7, seem to be of this type. In these cases, as in typical hereditary spherocytosis, splenectomy was associated with a marked reduction in the rate of haemolysis *in vivo*.

Inheritance of atypical congenital haemolytic anaemia. For various reasons the families of the present cases have not been exhaustively studied, and in only six of the ten families is there evidence of a familial incidence. In the other families there is no clinical history suggestive of anaemia, jaundice, or splenomegaly, and the blood of both parents of two of the patients (Cases 2 and 6) has been examined with negative or inconclusive results. The method of inheritance cannot be deduced from the scanty family data available in the present series, or in most of the previously published cases. In a few instances, however, the method of inheritance has been deduced. In the two families described by Rundles and Falls (1946) the disease appeared to be sex-linked, being present in males, and transmitted by females who suffered from a mild trait only. In Crosby's family (1950) the disease was not sex-linked, and appeared to be inherited as a dominant. In only one of our cases (Case 11) did there appear to be evidence of an anaemic trait (elliptocytosis) in other

apparently unaffected members of the family ; but only one parent was affected, and the case thus differed from that of Wyandt, Bancroft, and Winship (1941), already mentioned, in which both parents were affected with the elliptical-cell trait. It also differed from the cases of Mediterranean anaemia, in which both parents of a severely affected child are usually affected. Holst-Larsen's (1947) case histories suggest that elliptocytic haemolytic anaemia can certainly occur in persons heterozygous for the elliptical-cell trait. Presumably the genetic contribution of the other parent is a modifying factor, as already illustrated by the family studies carried out by Mason (1938), Wyandt, Bancroft, and Winship (1941), and Lendval (1949) on their patients. It seems likely that the difference between the expressivity of the gene for elliptocytosis in our Case 11 (severely anaemic) and in his brother (benign trait without anaemia) may be explained in this way. The apparently spontaneous appearance of anaemia in Cases 2, 6, and 12, where both parents have been examined and seem to be free from any abnormality, could be explained by mutation ; but in Cases 1 and 12 this explanation seems improbable. The fact that the other sibs were also affected suggests that their parents may have transmitted recessive deleterious genes which singly had no obvious effect, but which in combination caused serious abnormality. In patients 7, 8, and 9, all members of one family, the disease appeared to be inherited as a Mendelian dominant, as in typical hereditary spherocytosis (Race, 1942).

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Summary

Twelve patients with atypical congenital haemolytic anaemia are described with special reference to the blood findings. The disorder in each patient is believed to be genetically determined, although a familial incidence has been demonstrated in only six of the ten families concerned.

It is possible to classify these cases under five headings: Group 1, non-spherocytic congenital haemolytic anaemia (five cases) ; Group 2, variants of hereditary spherocytosis (four cases) ; Group 3, a type with macrocytosis and leg ulcers (one case) ; Group 4, a variant of familial elliptocytosis (one case) ; and Group 5, a type with 'triangular' red cells (one case).

Splenectomy did not benefit the four patients of Group 1 submitted to operation, nor the patients belonging to Groups 3 and 5. On the other hand, one of the patients of Group 2 and the patient belonging to Group 4 were greatly improved by splenectomy.

The disorders are thought to be due to inherent defects of the red cells which result in a diminished life-span *in vivo*. *In vitro*, in some cases at least, the cellular abnormality is reflected in an accelerated rate of spontaneous haemolysis and an abnormal alteration in osmotic fragility on incubation at 37° C. In

addition the red cells usually present striking and distinctive morphological abnormalities, which are illustrated in the present paper by a series of photomicrographs. Splenectomy, even if it does not appreciably affect the course of the disease, invariably causes some modification in the blood picture.

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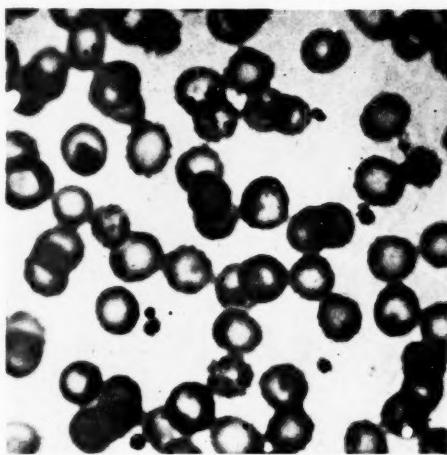


FIG. 3. Case 1. Photomicrograph of a peripheral blood film made 22 years after splenectomy. Nearly every red cell contains 'Pappenheimer' bodies (Leishman's stain, $\times 750$)

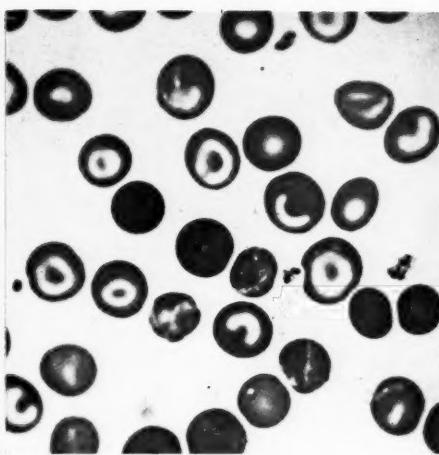


FIG. 4. Case 1. Photomicrograph of a peripheral blood film one month after the onset of serum hepatitis and seven weeks after a large volume of normal blood had been transfused. The patient's own red cells are identified by 'Pappenheimer' bodies and polychromasia. Only the transfused normal red cells were affected by the target-cell change (Jenner-Giemsa stain, $\times 960$)

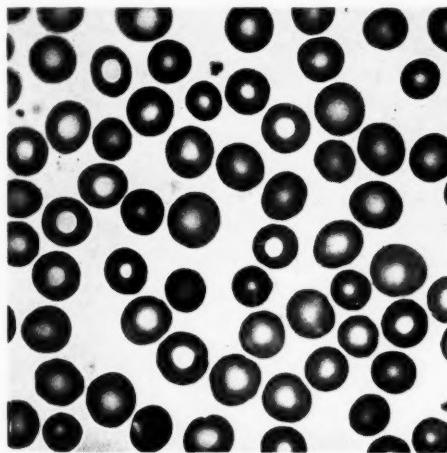


FIG. 5. Case 8. Photomicrograph of a peripheral blood film. There is a slight degree of microspherocytosis ($\times 960$)

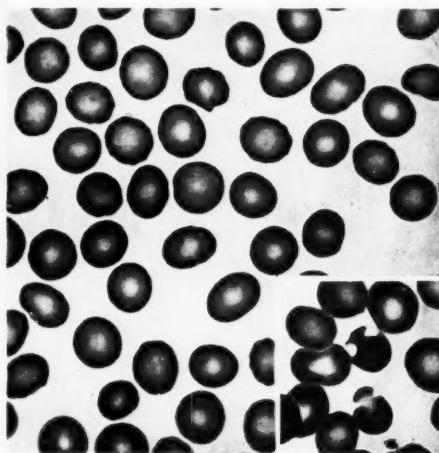


FIG. 6. Case 7. Photomicrograph of a peripheral blood film made before splenectomy. Many of the red cells are distinctly oval in shape. In the bottom right-hand corner are shown two 'pinched' cells from another area of the same film ($\times 960$)

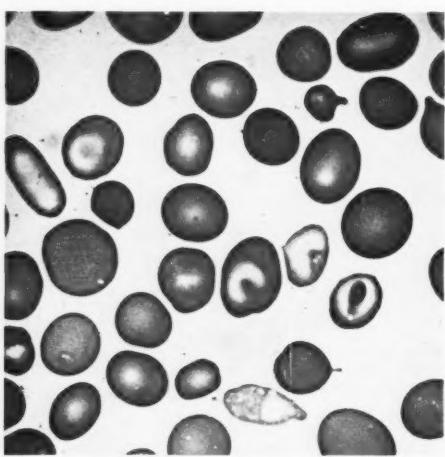


FIG. 7. Case 10. Photomicrograph of a peripheral blood film made two years after splenectomy. There is much variation in red-cell size, shape, and staining, with conspicuous macrocytosis and some target cells ($\times 960$)

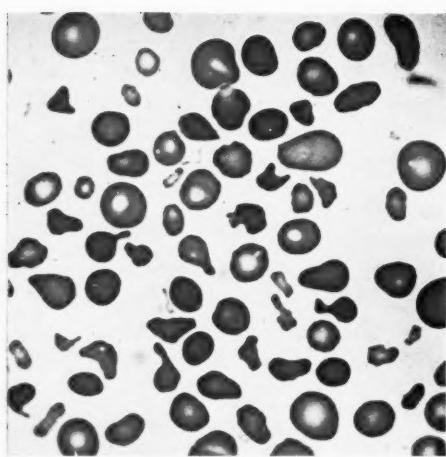


FIG. 8. Case 11. Photomicrograph of a peripheral blood film made two and a half years after splenectomy. The variation in red-cell size is extraordinary; minute irregular fragments of cells are present in large numbers ($\times 960$)

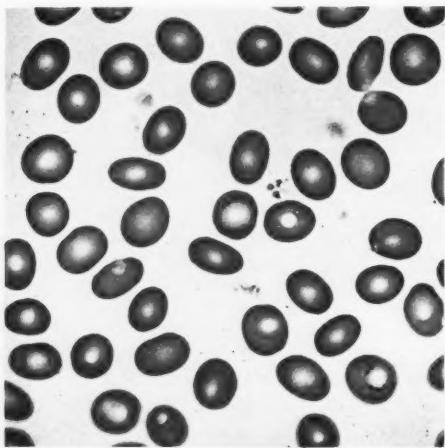


FIG. 9. Photomicrograph of a peripheral blood film made from the mother of Case 11. There is a moderate degree of elliptocytosis ($\times 960$)

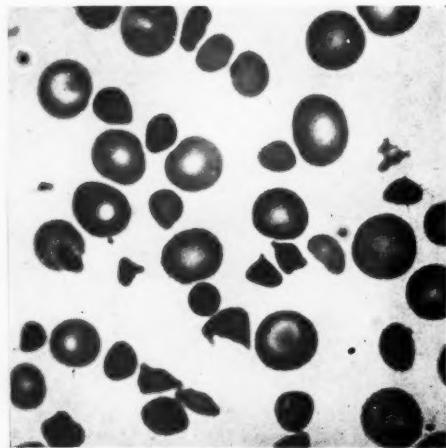


FIG. 10. Case 12. Photomicrograph of a peripheral blood film made 20 months after splenectomy. Small contracted corpuscles are conspicuous; some are almost triangular in shape ($\times 960$)

THE URINARY EXCRETION OF RADIOIODINE AS A CLINICAL TEST OF THYROID FUNCTION¹

BY RUSSELL FRASER, Q. J. G. HOBSON, D. G. ARNOTT
AND E. W. EMERY

(From the Postgraduate Medical School, Ducane Road, London, W. 12
and the M.R.C. Radiotherapeutic Research Unit)

THE diagnosis of hyperthyroidism or hypothyroidism may be made with certainty in some patients from obvious signs found on clinical examination, but often these signs do no more than suggest such a diagnosis. While the final diagnosis in such cases should emerge from observing the response to treatment, this response should not form the main diagnostic procedure, and further tests are needed. The estimations of greatest value for assessing thyroid function are those of the basal metabolic rate, the thyroid uptake of radioiodine, and the plasma protein-bound iodine or the plasma-cholesterol. As each test measures a different aspect of the thyroid function, each has its special usefulness, and in difficult cases the accuracy of diagnosis may be increased by using more than one. Radioiodine studies have now an established value as a means of measuring thyroid function, of which they offer more specific measures than do the basal metabolic rate and plasma-cholesterol determinations, on which the clinician commonly relies; but there is no agreement on the best simple procedure in the diagnostic use of radioiodine. Although measurements with radioiodine alone cannot give a direct estimate of the rate of thyroid hormone secretion, they assess the avidity of the thyroid for iodine. This is a direct index of thyroid cell activity, which usually closely corresponds to the rate of secretion of the hormone in the absence of recently administered antithyroid drugs, iodides, or thyroxine. The avidity of the thyroid for iodine can be studied either by direct measurements made over the gland, or indirectly by examination of the radio-iodine content of plasma or urine. Measurements made over the gland require a relatively large dose of radioiodine, and involve taking one or more measurements at predetermined times, which is a difficult requirement for large-scale clinical use. In our experience this method is best reserved for checking doubtful results obtained from the simpler procedure of examining the urinary excretion. The advantages of the urinary method are that it can be accurately carried out with a small dose of radioiodine, and that the test is easily applicable either to patients in bed or to out-patients. The objections to the procedure are the possibility of inaccurate urine collections, and that the excretion may be modified by renal or other non-thyroid factors; but from appropriate analysis of the urinary excretion it is possible to derive an index of thyroid function which is adequately independent of renal function, and will also help to check errors of collection.

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The simplest type of urinary test, the measurement of the total ^{131}I excretion in the 24 or 48 hours following administration of the radioiodine dose, does not show the detailed characteristics of the excretion in thyroid disease, and does not detect the slighter degrees of altered thyroid function. We therefore originally collected the urine in four samples (Arnott, Emery, Fraser, and Hobson, 1949), but we have since found that the three periods 0 to 8, 8 to 24, and 24 to 48 hours are equally satisfactory. Keating, Power, Berkson, and Haines (1947) described a mathematical analysis by which they obtained an index of thyroid uptake from a series of six to eight urinary measurements. We have used a simpler index, described below, which can be derived from the measurements obtained from the above three periods of urine collection. In the first section of the present paper we examine the validity of our method of interpretation, as judged by some theoretical curves and by results obtained from groups of proved thyroid, primary renal, and primary cardiac disease. We then review the first two years' results in order to assess the frequency of errors of all types and the practical usefulness of such a test.

Derivation of Indices of Thyroid Uptake from the Urinary Excretion of ^{131}I

The simplest interpretation of the excretion process has been described by Keating, Power, Berkson, and Haines (1947), and is the basis of their analysis. It is supposed that the dose of labelled iodide comes rapidly into equilibrium with normal iodide circulating in the plasma, and is thereafter removed by the thyroid and kidneys acting in competition on this pool at constant rates of extraction. The amount reaching the urine within any time would then depend on these two rates in accordance with the following equation:

$$Ut = \frac{k_u}{k_u + k_t} (1 - e^{-(k_u + k_t)t}), \quad (1)$$

where Ut = percentage of dose excreted in t hours; k_t = rate of removal of ^{131}I by the thyroid, expressed as fraction of the iodide pool per hour; k_u = rate of removal of ^{131}I by the kidneys, similarly expressed.

This equation leads to an excretion curve which rises to a limiting value, determined solely by the ratio of k_u to k_t , irrespective of their actual magnitudes, at a rate which depends on the sum of k_u and k_t irrespective of the ratio. A high value for the excretion might result either from high k_u or low k_t . If this theory were completely valid it would be possible to calculate both k_u and k_t from the amount of radioiodine excreted at any two different times. These values could then be derived from the measurements at 8 hours and 48 hours with the aid of Figs. 1 and 2. But the process is complicated by the reappearance in the circulation, and thence in the urine, of some of the radioiodine which has already been once removed by the thyroid. The curve of urinary excretion consequently continues to rise in its later phase beyond the values expected on the simple theory: in normal subjects within the 0-48-hour period this discrepancy is slight, but it is more serious in hyperthyroid patients, in whom even the 0-8-hour excretion may appreciably exceed the theoretical value. By taking frequent early samples, Keating, Power, Berkson, and Haines (1947) were able to apply their analysis successfully even to thyrotoxic patients, and found good correlation between k_t so measured and the rate of thyroid uptake or clearance measured over the neck. By taking our first sample as late as eight hours after administration of the dose, we avoided the clinical difficulties

inherent in making accurate short-period collections, but were debarred from using Keating's analysis in hyperthyroid cases. For this reason an alternative treatment of the data was needed.

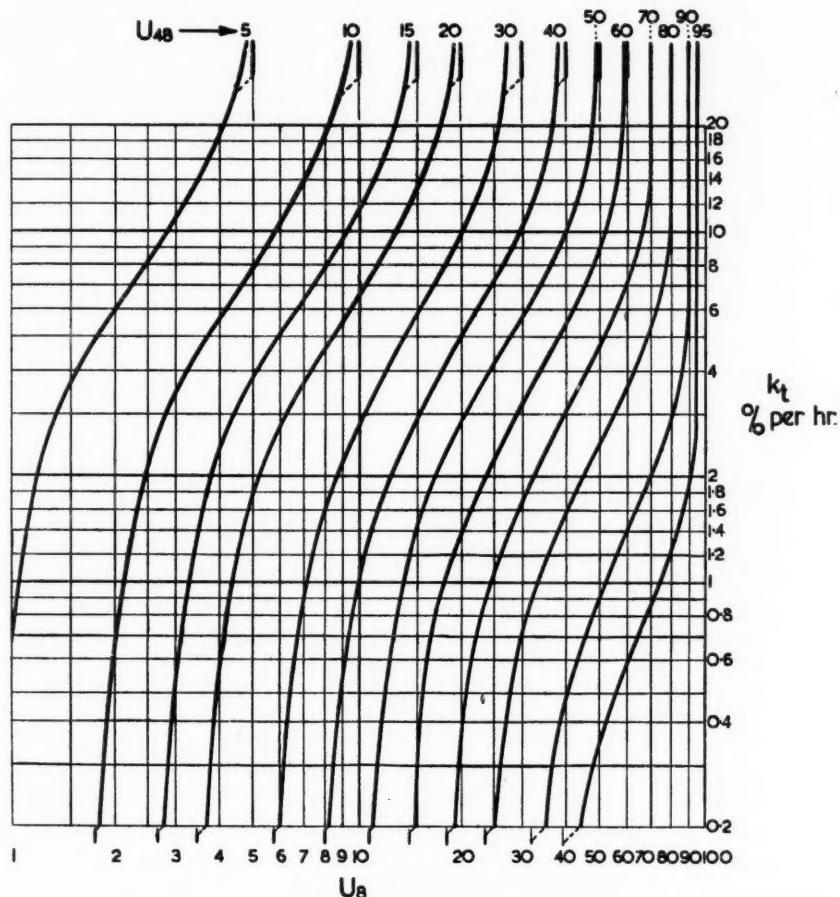


FIG. 1. Graph for deriving the k_t index of thyroid uptake from the 0-8 and 0-48-hour percentage excretion figure.

The curves show the relationship between k_t and the 0-8-hour excretion at fixed values of the 0-48-hour excretion. To use the diagram a point is selected on the horizontal scale corresponding to the 0-8-hour excretion; then by moving vertically upwards a point is found which, by interpolation between the curves, corresponds to the 0-48-hour excretion. Opposite this point on the right-hand vertical scale is to be found the value of k_t corresponding to these values of the 0-8 and 0-48-hour excretion.

We have found that the 8-24-hour period is sufficiently independent of re-excretion to be a valid index of increased thyroid activity, even in severe thyrotoxicosis. Consequently the reciprocal $\frac{1}{(8-24)}$ should be a good index of thyroid activity. With low excretion due to renal deficiency, this index may be high without thyroid disorder. This error may be diminished by multiplying

the index by the factor $\frac{(0-8)}{(0-48)}$. The value of this factor is determined mainly by the total blood clearance ($k_u + k_t$), and decreases with a lowering of either k_u

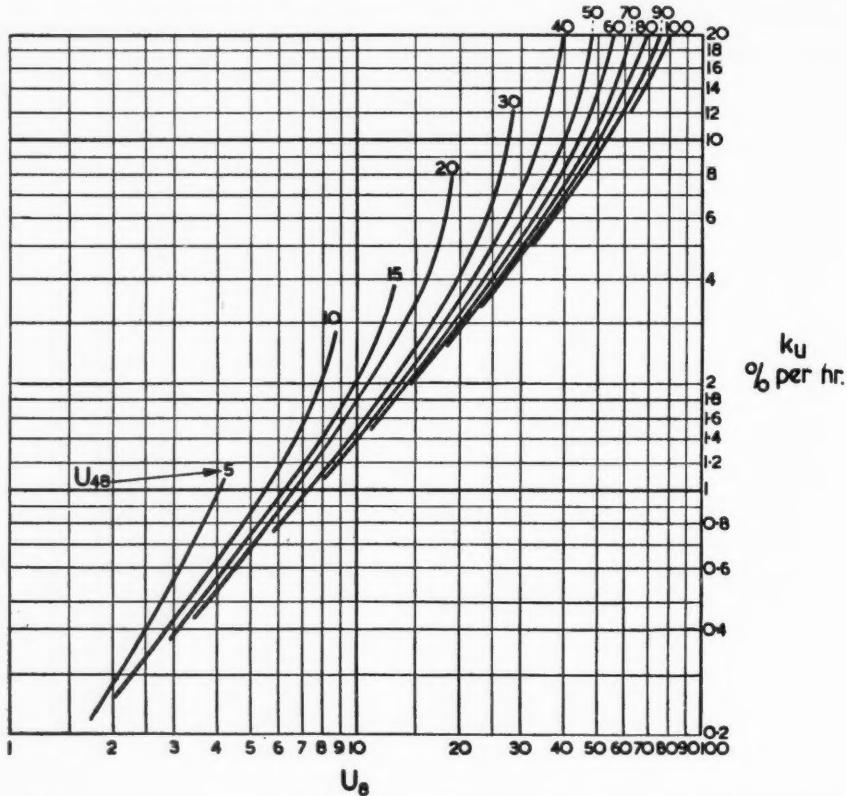


FIG. 2. Graph for deriving the k_u index of renal iodide extraction from the 0-8 and 0-48-hour percentage excretion figures.

The curves are used as described under Fig. 1 for deriving k_t .

or k_t . Hence, if k_u should be abnormally low, a correction can be made for the misleadingly high value given by $\frac{1}{(8-24)}$. For these reasons we tested the following index, introducing the factor 100 to avoid fractions:

$$T = \frac{(0-8 \text{ hrs. \%}) \times 100}{(8-24 \text{ hrs. \%}) \times (0-48 \text{ hrs. \%})}. \quad (2)$$

In order to see whether such an index might be expected to be independent of the renal condition, equation (1) was used to calculate U_8 , U_{24} , and U_{48} , and thence T , in the range of conditions likely to be met with in practice; and in Fig. 3 these values of T are plotted against k_u for various values of k_t . Provided that there is no gross renal abnormality, Fig. 3 shows that the range of values of k_t corresponding to a given T value should not be sufficient to invalidate the

diagnosis. T may underestimate a decrease in thyroid function, but should lead to no serious clinical errors; this point can be checked safely by deriving k_t from the graph in Fig. 1. Those interested in the statistical treatment of results will notice that the curves corresponding to given values of k_t are roughly equally spaced on a logarithmic scale, so that for any group of patients $\log T$ may be expected to be distributed in a similar manner to k_t , that is, probably in a normal distribution. We conclude that T should reflect thyroid uptake

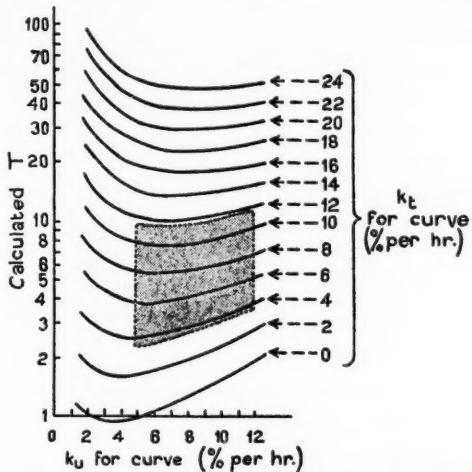


FIG. 3. The 'T' values of theoretical excretion curves, based on equation (1) (p. 100), over the range of k_u and k_t likely to be met in clinical practice. The shaded area covers the range of k_t and k_u found among our normal subjects.

$$T = \frac{(0-8 \text{ hrs. \%}) \times 100}{(8-24 \text{ hrs. \%}) \times (0-48 \text{ hrs. \%})}.$$

sufficiently independently of renal function for routine clinical use. An alternative index, k_t , derived from Fig. 1, is also a valid index of thyroid uptake, provided it is not used in cases of suspected hyperthyroidism.

Method of Test

Preparation of the patient. The metabolism of iodine by the thyroid may be altered for two or three months after treatment with iodine, thyroid extract, or antithyroid drugs, and for up to two years after the diagnostic use of contrast media containing organic iodine. Before commencing the test the clinician must therefore obtain details of previous investigations or treatment with such drugs, the recent use of which may invalidate the test results.

Administration of the test. After a fast of at least three hours, the dose of 10 μ c. of ^{131}I with 10 μg . of iodide carrier is given. The dose is drunk directly from the dose bottle, which is washed twice, and the washings are drunk to ensure that the whole dose is swallowed. The patient and nursing staff are carefully instructed, and out-patients are supplied with panniers containing three labelled Winchester quart bottles, and with printed instructions to ensure

accurate urine collections. The urine is collected from the time that the dose is drunk, using one bottle for each of the three periods 0 to 8, 8 to 24, and 24 to 48 hours. The importance of emptying the bladder precisely at the end of each period, especially at 8 hours, and of not losing urine when the bowels are opened, is explained to the patient.

Assay of samples. The measurement of the excreted radioiodine is made directly on each specimen bottle by detection of emitted γ -rays. The volume of urine in each bottle is adjusted to approximately two litres, and the bottle is then set in a ring of six γ -sensitive Geiger-Müller tubes connected in parallel. The response is indicated on a ratemeter. The apparatus has been described by Veall and Vetter (1952). The figure for each sample is then compared with that obtained from a standard containing one-tenth of the administered dose, diluted to the same volume, in a similar bottle. The radioactivity of each sample is finally expressed as a percentage of the administered dose. The method is simple, accurate, reliable, and quick; a complete measurement of one patient's samples may be made in less than five minutes.

Derivation of indices of thyroid uptake. (1) Routine interpretation is by the index T , calculated from
$$\frac{(0-8 \text{ hrs. } \%)\times 100}{(8-24 \text{ hrs. } \%)\times (0-48 \text{ hrs. } \%)}.$$
 (2) The index k_v , the percentage removed per hour by non-renal processes, can be obtained from the 0-8 and 0-48-hour excretion figures by using Fig. 1, and k_u by using Fig. 2.

Test for excretion of excess of iodide. When iodides are known to have been taken previously, or when an unexpectedly high excretion of radioiodine has been found, the simple qualitative test detailed in the Appendix has recently been applied to the 24-48-hour urine sample. This test is adjusted to indicate a total daily iodide excretion either exceeding 0.5 mg. or under 0.1 mg. per 24 hours, and so some apparently erroneous results can be identified as due to excessive iodide intake. This test has been found negative at the 0.1 mg.-per-24-hours level in a large series of normal test results.

Results

Source of the data. In this paper we present the results of all our tests carried out in the years 1948 to 1950. In each case the final diagnosis has been established by reviewing, at least six months after the test, all the clinical findings, including in many cases the response to treatment. Verified errors, and tests made during treatment or after drugs, have been excluded from the main analysis, which covers the remaining 397 tests. Reference to Table I shows that this group was composed mostly of diagnostic tests made on patients suspected of thyroid disease. The group also includes some tests of patients with normal thyroid function, made in order to assess the normal range and the influence of renal and cardiac disease on the test results.

I. The interpretation of the test

1. *Relative efficiency of indices.* We have compared the diagnostic value and specificity, as thyroid indices, of the 0-48 and 8-24-hour urinary excretions,

TABLE I
Clinical Grouping of All Tests Analysed (1948-50)

	<i>Reason for test and final diagnosis</i>	<i>Number of tests</i>
I. MAIN ANALYSIS:		
A. Chosen patients without thyroid disease:	.	65
Normal	.	32
Renal disease	.	23
Heart disease	.	3
Other miscellaneous cases	.	7
B. Patients suspected of thyroid disorder:	.	
1. ?Hyperthyroidism:	.	221
(a) Hyperthyroidism confirmed clinically (83):	.	
Exophthalmic Graves' disease	{ severe	25
	{ mild*	31
Toxic goitre without eye signs	{ severe	16
	{ mild	11
(b) Hyperthyroidism unconfirmed clinically (138):	.	
Ophthalmic Graves' disease (without clinical hyperthyroidism)	.	8
Non-toxic goitre with neurosis	.	36
Non-toxic goitre	.	36
Neurosis	.	31
Heart disease	.	15
Miscellaneous	.	12
2. ?Non-toxic goitre:	.	49
(a) Confirmed (43):	.	
Diffuse goitre	.	11
Multiple nodular goitre	.	18
Solitary nodule		
active (proved by plot of local uptake)	.	3
inactive	.	5
activity not determined	.	6
(b) Other conditions (6):	.	
Chronic thyroditis (lymphadenoid type)	.	3
Goitre with myxoedema	.	1
Non-thyroid tumour	.	2
3. ?Myxoedema and hypothyroidism:	.	59
(a) Clinically confirmed myxoedema (32):	{ severe	23
	{ mild	9
(Primary myxoedema in 20 patients, post-operative in 6, due to Simmonds's disease in 4)	.	
(b) Goitrogen myxoedema, confirmed after withdrawal	.	4
(c) Myxoedema unconfirmed (23):	.	
Heart disease	.	5
Psychoneurosis	.	4
Mild Simmonds's disease	.	4
Other endocrine disease	.	8
(Dwarfism 3, eunuchoidism 2, obesity 1, haemochromatosis 1)	.	
Undiagnosed	.	2
4. Other conditions:	.	
Subacute thyroiditis	.	1
Functioning metastases from thyroid carcinoma†	.	2
Total for main analysis	.	397
II. NOT INCLUDED IN MAIN ANALYSIS		
Tests made during treatment or after drugs	.	215
Confirmed errors in test	.	49
		661

* The only toxic solitary nodule was in this group.

† Only carcinomas with functioning metastases were assessed by the urinary tests; other thyroid carcinomas were assessed only by a localization test.

and the derived indices T and k_t (Fig. 4). This comparison has been based on results obtained with five groups of patients, comprising 32 normal subjects, 83

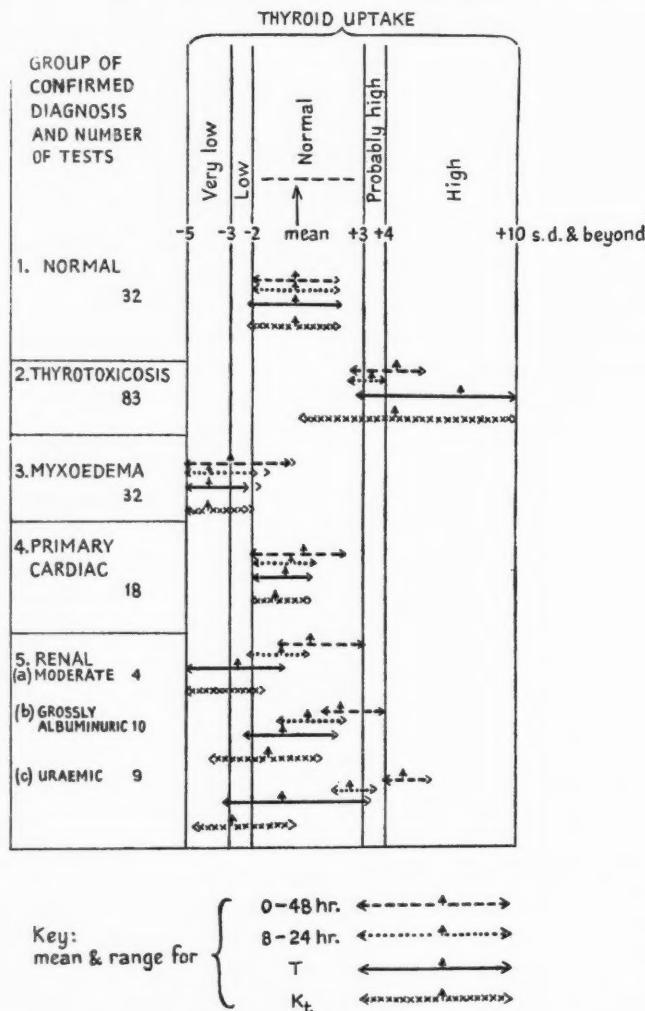


FIG. 4. The four urinary indices of thyroid uptake compared in groups of patients with confirmed clinical diagnoses.

For each group are shown the mean and range values of the four indices studied—the 0–48-hour and 8–24-hour excretions, and the derived indices T and k_t . The scale for each index has been shown in terms of the normal range, i.e. in standard deviations of the normal group above and below its mean, and arranged so that deviation to the left implies a decrease of thyroid function, and deviation to the right an increase. Since three of the cases of myxoedema showed normal uptake by all four indices, this group has been shown with two upper ranges—that for the whole group and that for ‘myxoedema with abnormal uptake’, excluding these three cases.

cases of confirmed hyperthyroidism, 30 of confirmed myxoedema, 18 of primary heart disease, and 23 of primary renal disorder. The mean value and range of the four thyroid indices referred to above have been shown for each group. Since three of the tests in cases of myxoedema showed normal uptake by all four indices, this group has been shown with two upper ranges—that for the whole group, and that for the group omitting these three tests. The latter limit is the more useful for comparing the relative efficiency of the indices. The 0-48-hour excretion is evidently sensitive to increased thyroid uptake, but similar values may occur in severe renal disease, while normal values may be found in some cases of myxoedema. The same objections apply in much lesser degree to the 8-24-hour excretion. Though in non-uraemic renal disease and in cardiac disease the 8-24-hour excretion can be relied upon to give a normal value, it extends the 'myxoedema with abnormal uptake' group into the normal range (three cases). k_t seems an efficient index with decreased thyroid function, but not with hyperthyroidism, in which it sometimes gives a normal result. The T index differentiates the hyperthyroid group from the normal range better than any other index, and its sensitivity to hypothyroidism approximates to that of the k_t index. In all cases but one of 'myxoedema showing abnormal uptake' both T and k_t values were abnormal; the exceptional T value was barely inside the normal range. If the test can recognize myxoedema, it will usually do so by either index. On examination of the full distribution of each index for the severe and mild myxoedema groups, as shown in Fig. 5 for T , the k_t index appeared to correlate somewhat more closely with the clinical severity of the myxoedema.

Conclusion. The index T is evidently a clinically valid index of thyroid function, and the 8-24-hour excretion a useful check except in lowered thyroid function, when k_t can be used for this purpose. Although k_t is more reliable when thyroid or renal function is impaired, both T and k_t indices usually reveal abnormally low uptakes; but when the indication of hypothyroidism is doubtful, k_t should be derived and the interpretation based thereon.

2. Confirmation and frequency of errors. The several indices of thyroid function available from the test provide a simple means of checking the indications of error revealed by unusual subdivision between the samples. By reference to Table II thyroid uptakes may be classified in five ranges by the T index, and also by either the 0-48-hour, the 8-24-hour, or the k_t value; the T index should agree with any of these checks unless there has been error or severe renal disease. In practice the T value is checked with the 8-24-hour interpretation, except in the case of known renal disorder or of results indicating hypothyroidism, when it is checked with the k_t value. Questioning of the patient will usually confirm such errors; if not, anomalies of bladder-emptying may be suspected. A repetition of the test usually gives the final confirmation. The slighter deviations from normal may be more precisely checked at a subsequent test by assessing the thyroid uptake directly over the gland, when hypothyroidism is suspected or when accurate urinary collections are impracticable. Among our 661 tests from 1948 to 1950 we thus found 49 confirmed errors (7.3 per cent.).

mainly due to inaccurate collections. We have found that errors from urinary tests are greatly reduced when out-patients are personally entrusted with the accuracy of collection, provided that they have been carefully instructed and supplied with convenient containers for the sample bottles.

3. *Results in patients with normal thyroids.* (1) *Normal subjects* (Table III). In Table III is shown the range of 32 results from 17 healthy adults and 15

TABLE II
The Limits of the Five Clinical Ranges of Thyroid Uptake

(For interpretation of test results)

<i>Range of thyroid uptake</i>	<i>Urinary excretion (% of dose given)</i>			<i>Limits for</i>	
	<i>0-48 hrs.</i>	<i>8-24 hrs.</i>	<i>T</i>	<i>log T</i>	<i>k_t</i>
High = beyond	32.0	4.0	17.4	1.240	..
Probably high = from normal to	38.4	6.2	12.8	1.108	11.0
Normal = within	73.2	21.0	2.8	0.448	4.0
Low = from normal to	81.9	24.7	2.1	0.316	2.0
Very low = beyond					
<i>Normal group values:</i>					
mean	55.8	13.6	5.15	0.712	6.9
standard deviation	± 8.7	± 3.7	..	± 0.132	± 1.91
<i>Basis of ranges</i>					
<i>Excretion figures</i>		<i>T</i>		<i>k_t</i>	
Normal	Mean ± 2 s.d.	Mean -2 to +3 s.d.	Observed range (in round numbers)		
High	That defined by the confirmed thyrotoxic group				
Very low	Beyond 3 s.d. below normal mean				Below half lower limit of normal

patients chosen as having normal thyroid function. No differences could be detected between the results in these two sub-groups. A further group of adult normal subjects was abstracted from our results, consisting of all those who had clinically normal thyroids and were tested for reasons other than suspicion of thyroid disorder. The results from this group closely approximate to those of the former group, and so confirm the normal standard values for our area of the country.

(2) *Renal impairment due to primary renal disease* (Fig. 4 and Table III). The urinary excretion was examined in 23 patients with primary renal disease, who were chosen to include typical instances of (a) lesser renal disease, (b) gross albuminuria with or without oedema, but without uraemia, and (c) uraemia (blood-urea over 100 mg. per 100 ml.). The renal disease was either malignant hypertension, nephritis (acute, subacute, or chronic), or acute tubular nephrosis. The results in Table III show that the renal clearance of iodide was impaired in almost all instances (k_u mean 2.5 per cent., range 0.1 to 7.4 per cent. per hour; compared with the normal k_u , mean 8.4 per cent., range 4.9 to 12.0 per

TABLE III

Chosen Normals and Main Groups with Confirmed Thyroid, Renal, or Cardiac Disorders; Results of Urinary Excretion Tests

Mean values and standard deviations (ranges in parentheses)

	Group	Number of patients	Excretion of ^{31}I (% of administered dose) in			Factors calculated therefrom		
			Tests	0-8 hrs.	8-24 hrs.	24-48 hrs.	T	$\log T$
1. Normal subjects	.	10 F 22 M } 32	38.7 (26.0-49.5)	13.6 (6.0-19.1)	3.2 (0.1-0.4)	55.8 ± 8.7 (37.6-68.7)	(5.15) (2.72-10.0)	0.712 ± 0.132 (0.435-1.00)
2. Thyrotoxicosis with eye signs:								
(a) severe	.	24	25	11.2 (3.0-27.8)	1.7 (0.4-4.9)	1.5 (0.1-3.2)	14.3 (5.7-32.0)	..
(b) mild	.	30	31	11.7 (3.6-25.9)	1.6 (0.1-3.0)	1.7 (0.3-4.2)	15.4 (6.4-28.5)	..
3. Toxic goitre (no eye signs):								
(a) severe	.	15	16	14.3 (2.2-27.4)	2.0 (0.6-3.6)	1.5 (0.5-4.3)	16.4 (6.2-31.3)	..
(b) mild	.	11	11	16.1 (8.4-26.9)	2.1 (1.3-3.5)	1.9 (0.3-4.6)	20.1 (12.0-31.3)	..
4. Myxoedema:								
(a) severe	.	20	22*	35.6 (19.3-58.9)	27.0 (23.0-40.9)	13.5 (4.2-21.8)	76.8 (60.0-97.0)	..
(b) mild	.	8	9	31.3 (22.5-45.3)	26.2 (18.0-39.7)	11.5 (3.0-29.4)	74.3 (58.8-93.4)	..
(c) due to goitrogen (after withdrawal)	.	4	4	5.0 (3.0-8.8)	1.2 (0.7-2.5)	1.1 (0.3-2.1)	7.3 (5.8-9.9)	..
5. Renal disease:								
(a) slight albuminuria	.	4	4	21.7 (6.2-37.6)	16.0 (9.4-21.6)	11.4 (9.4-21.2)	49.1 (28.1-61.4)	..
(b) gross albuminuria ± oedema	.	10	10	16.8 (3.6-29.7)	11.7 (5.7-16.3)	6.3 (2.5-1.1)	37.8 (21.0-46.7)	..
(c) uremia (blood urea > 100 mg. %) (± oedema, ± gross albuminuria)	.	9	9	3.5 (0.9-10.4)	5.1 (0.9-8.1)	4.3 (1.1-9.1)	13.0 (2.9-20.6)	..
6. Heart disease:								
(a) without heart failure	.	9	9	31.3 (17.2-50.9)	14.6 (10.0-19.5)	3.4 (0.8-5.8)	49.2 (38.0-72.0)	..
(b) with heart failure	.	9	9	30.1 (13.6-49.9)	14.7 (10.9-19.0)	6.58 (1.7-11.3)	50.2 (36.1-67.1)	..

* One exceptional test result, which could not be repeated, may have been due to error and is not included. Its values were 0-8 hrs. 15 per cent., 8-24 hrs. 13 per cent., 24-28 hrs. 3.8 per cent., 0-48 hrs. 31.8 per cent., $\log T$ 0.560.

Mean values and standard deviations (ranges in parentheses)

Factors calculated therefrom

 k_4 k_6 k_8 k_{10} k_{12} k_{14} k_{16} k_{18} k_{20} k_{22} k_{24} k_{26} k_{28} k_{30} k_{32} k_{34} k_{36} k_{38} k_{40} k_{42} k_{44} k_{46} k_{48} k_{50} k_{52} k_{54} k_{56} k_{58} k_{60} k_{62} k_{64} k_{66} k_{68} k_{70} k_{72} k_{74} k_{76} k_{78} k_{80} k_{82} k_{84} k_{86} k_{88} k_{90} k_{92} k_{94} k_{96} k_{98} k_{100} k_{102} k_{104} k_{106} k_{108} k_{110} k_{112} k_{114} k_{116} k_{118} k_{120} k_{122} k_{124} k_{126} k_{128} k_{130} k_{132} k_{134} k_{136} k_{138} k_{140} k_{142} k_{144} k_{146} k_{148} k_{150} k_{152} k_{154} k_{156} k_{158} k_{160} k_{162} k_{164} k_{166} k_{168} k_{170} k_{172} k_{174} k_{176} k_{178} k_{180} k_{182} k_{184} k_{186} k_{188} k_{190} k_{192} k_{194} k_{196} k_{198} k_{200} k_{202} k_{204} k_{206} k_{208} k_{210} k_{212} k_{214} k_{216} k_{218} k_{220} k_{222} k_{224} k_{226} k_{228} k_{230} k_{232} k_{234} k_{236} k_{238} k_{240} k_{242} k_{244} k_{246} k_{248} k_{250} k_{252} k_{254} k_{256} k_{258} k_{260} k_{262} k_{264} k_{266} k_{268} k_{270} k_{272} k_{274} k_{276} k_{278} k_{280} k_{282} k_{284} k_{286} k_{288} k_{290} k_{292} k_{294} k_{296} k_{298} k_{300} k_{302} k_{304} k_{306} k_{308} k_{310} k_{312} k_{314} k_{316} k_{318} k_{320} k_{322} k_{324} k_{326} k_{328} k_{330} k_{332} k_{334} k_{336} k_{338} k_{340} k_{342} k_{344} k_{346} k_{348} k_{350} k_{352} k_{354} k_{356} k_{358} k_{360} k_{362} k_{364} k_{366} k_{368} k_{370} k_{372} k_{374} k_{376} k_{378} k_{380} k_{382} k_{384} k_{386} k_{388} k_{390} k_{392} k_{394} k_{396} k_{398} k_{400} k_{402} k_{404} k_{406} k_{408} k_{410} k_{412} k_{414} k_{416} k_{418} k_{420} k_{422} k_{424} k_{426} k_{428} k_{430} k_{432} k_{434} k_{436} k_{438} k_{440} k_{442} k_{444} k_{446} k_{448} k_{450} k_{452} k_{454} k_{456} k_{458} k_{460} k_{462} k_{464} k_{466} k_{468} k_{470} k_{472} k_{474} k_{476} k_{478} k_{480} k_{482} k_{484} k_{486} k_{488} k_{490} k_{492} k_{494} k_{496} k_{498} k_{500}

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cent. per hour). The 0-48-hour excretion was lowered to the levels found in thyrotoxicosis only among the two severe groups; but in contrast to thyrotoxicosis, the lowering was mainly in the 0-8-hour period. The 8-24-hour excretion was down to the 'high thyroid uptake' range in only one case outside the uraemic group. In all these patients k_t was in the lower normal range or below. The T values were also in the same range, though somewhat higher, but gave no clinically false indications of thyroid abnormality except in one uraemic patient. Clinically mild renal disease does not alter the excretion of radioiodine beyond the normal range, and in renal disease without uraemia the indices k_t and T should be normal.

(3) *Heart disease* (Fig. 4 and Table III). Eighteen patients with heart disease have been tested; nine patients were tested when in congestive heart failure. Though only three patients were chosen for testing as instances of obvious primary heart disease, subsequent clinical observation of the other 15 patients excluded thyroid disease, and confirmed the presence of hypertensive heart disease, valvular disease, or ischaemic heart disease. No instances of pulmonary heart disease have been included. The mean values of the T and k_t indices and the 8-24-hour excretion in these cases implied a lower thyroid uptake than that of patients with normal thyroid function, but all values were within the normal range; the 0-48-hour excretion was less reliable, the excretion exceeding the normal range in one patient and falling below this range in five patients. There was no significant difference between patients with heart failure and those without heart failure.

4. *The five clinically significant ranges of thyroid uptake, and the interpretation of test results.* Fig. 5 shows the distribution of T index values obtained from the groups of confirmed hyperthyroidism and myxoedema, and from the normal subjects, and Table III the other values obtained from these tests. It is clear from Fig. 5 that the test, and especially the T index, is very sensitive in recognizing hyperthyroidism, but insufficiently sensitive for the certain diagnosis of all cases of myxoedema. We have therefore defined the normal range of T values as from -2 to $+3$ times the standard deviation from the normal mean. For the excretion values we have defined the normal range as the mean \pm twice the standard deviation. The k_t index showed skewness towards higher values in the normal group, and consequently we have used the observed range in round numbers as defining the normal limits. For 82 of the 83 tests made on patients with confirmed thyrotoxicosis the T values lie above 17.4, or more than 4 times the standard deviation above the normal mean (Fig. 5); and the 8-24-hour and 0-48-hour excretion values lie below 4 per cent. and 32 per cent. respectively (Table III). These ranges, typical of confirmed thyrotoxicosis, have therefore been defined as high uptakes; with all the three indices they are well separated from the normal limits, as defined above, by a lesser range of increased uptake, which has therefore been defined as 'probably high'. The one exceptional 'confirmed thyrotoxic' result gave 8-24-hour and 0-48-hour excretion values within the 'high' range, so that its 'probably high' T value may be due to a minor collection error. The myxoedema range, however, begins at the lower limit of

the normal, and two ranges of low uptake can be usefully defined—‘very low’ uptake for values beyond three times the standard deviation, and ‘low’ uptake between two and three times the standard deviation, below the normal mean. In the case of k_t we have classed as ‘very low’ values which are less than half the lower limit of the normal range. The actual values corresponding to these five ranges for the T index, the 8–24-hour and 0–48-hour excretions, and the k_t

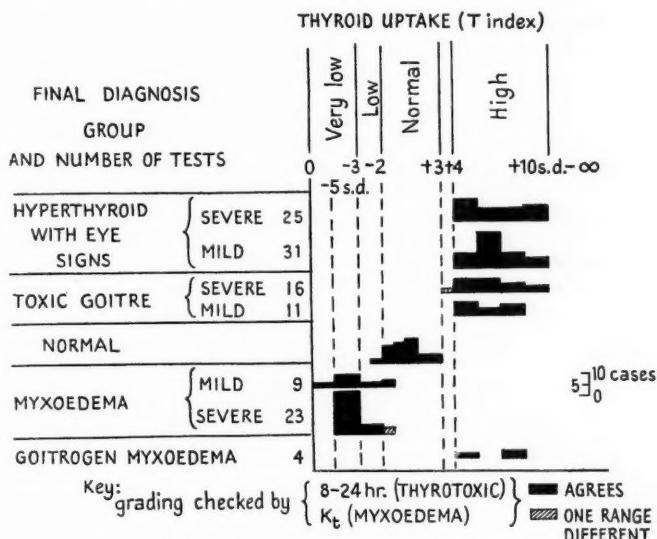


FIG. 5. Results in normal subjects and in groups with confirmed abnormal thyroid function.

index, are shown in Table II, and this Table has been used as the basis of diagnostic interpretation. Only ‘high’ uptake confirms hyperthyroidism; either ‘very low’ or ‘low’ uptake can confirm myxoedema, though obviously the reliability is greatest with ‘very low’ uptake; and myxoedema cannot safely be excluded unless, perhaps, the uptake is above the normal mean.

II. Clinical application of the test

The following analysis is based on the groups of patients originally tested for suspected thyroid disease, and aims to assess the help which the test might offer in the diagnosis of hyperthyroidism, non-toxic goitre, and myxoedema.

1. *Patients suspected of hyperthyroidism* (221 tests; Figs. 5 and 6; Table III). All these patients have been finally classed clinically as either ‘hyperthyroidism confirmed’ (83) or ‘hyperthyroidism unconfirmed’ (138), and sub-grouped according to final diagnosis as shown in Table I. The results for the 83 patients with ‘hyperthyroidism confirmed’ are summarized in Fig. 5 and Table III. The ‘high’ uptake range has been defined from this group as the one typical of thyrotoxicosis; both the 8–24-hour excretion and the T index were in this ‘high’ thyroid uptake range in all cases, excepting one presumed error in which only

the 8-24-hour value was 'high'. The initial clinical diagnosis of hyperthyroidism had been certain in only one-quarter of these 83 confirmed thyrotoxic patients; many had only slight clinical symptoms and signs. There was little rise in the T index with increasing clinical severity of the hyperthyroidism. The T index

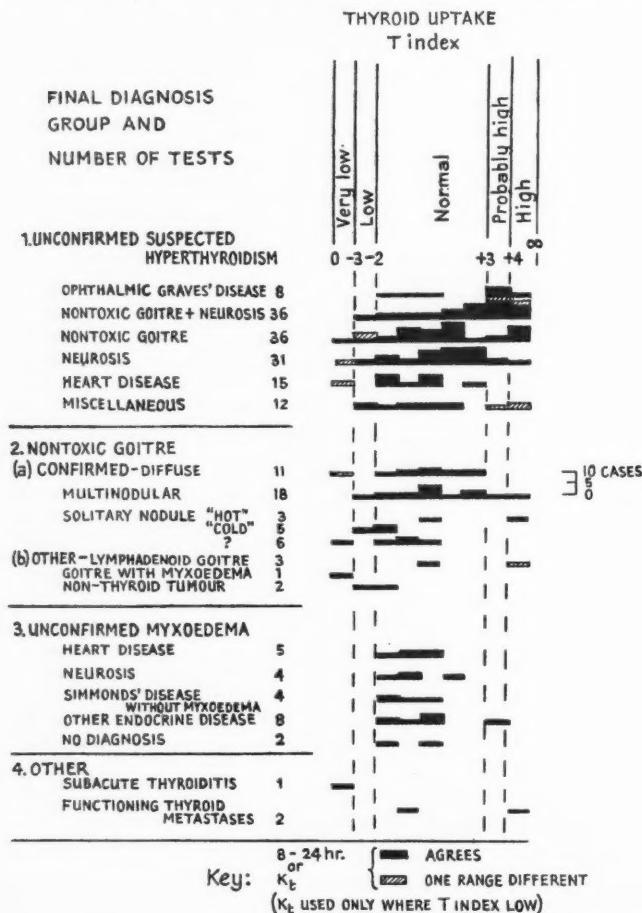


FIG. 6. Results in groups without confirmed abnormal thyroid function.

was, however, slightly higher in patients with exophthalmic goitre than in those with toxic goitre, and also slightly higher in the clinically severe than in the mild sub-groups. The basal metabolic rates lower than +35 per cent. showed a rough correlation with the T index of thyroid uptake (Fig. 7). When the basal metabolic rate was greater than this, the T index was not correspondingly higher; this is possibly because the T index, when well above the normal range, increasingly underestimates the thyroid uptake. The increase in thyroid uptake showed little relationship to the patient's age (Table IV); the highest mean

uptakes were found in the fourth and fifth decades, when the disease is most severe. No correlation was found between the T index and the duration of the patient's preceding thyrotoxic symptoms.

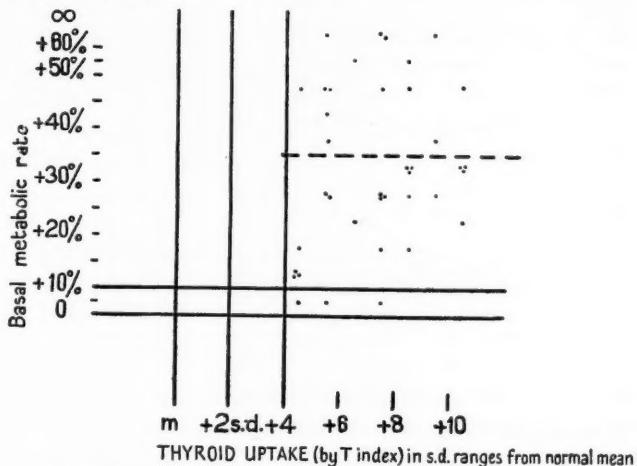


FIG. 7. Correlation of basal metabolic rate and thyroid uptake among female thyrotoxic patients.

TABLE IV

All Female Patients with Confirmed Thyrotoxicosis ranged by Age; Results of Test of Urinary Excretion of ^{131}I

Thyroid uptake as mean log T for group
(Number of cases in parentheses)

Age range (years)	Exophthalmic goitre	Toxic goitre
10-19 . . .	1.741 (2)	..
20-29 . . .	1.608 (12)	1.456 (3)
30-39 . . .	1.787 (15)	1.660 (3)
40-49 . . .	1.729 (10)	1.851 (2)
50-59 . . .	1.611 (5)	1.722 (6)
60 and over (1)	1.60 (8)

The individual T values for all the 138 patients in whom hyperthyroidism was not confirmed are shown in Fig. 6. Eighty-nine of the 138 results were normal. The cross-hatching indicates cases in which errors in the test are suspected on the grounds that the T index disagrees with the 8-24-hour excretion or k_t values. There were 14 such tests, and so error might account for eight of the increased and for six of the lowered uptakes. There remain five other 'low' results, and these we suspect to be due to previous administration of iodides. There also remain 30 other 'high' or 'probably high' results. Of these 22 were associated with non-toxic goitre (with or without neurosis), five with ophthalmic Graves' disease, and three with neurosis. It may be noted that the two non-toxic

² Showing the ophthalmic features of Graves' disease without clinically definite hyperthyroidism.

goitre patients with solitary nodules showed 'high' thyroid uptake; and also that a tendency to raised thyroid uptake is a general feature of the neurosis group, only eight of the 31 cases having T values below the mean of the normal range.

Reviewing the whole group of 221 cases of suspected hyperthyroidism, we have found 89 normal results, none of which was associated with confirmed hyperthyroidism. Here it must be noted that patients known to have had previous relevant drug treatment have been excluded from the analysis. There were 101 'high' uptakes, of which 82 were in patients with confirmed thyrotoxicosis, and 14 in patients finally diagnosed as having ophthalmic Graves' disease, non-toxic goitre with or without neurosis, or neurosis. There were 16 'probably high' uptakes in patients also finally diagnosed in these same three categories. Thus all the unconfirmed thyrotoxic patients showing either 'high' or 'probably high' uptakes showed either ophthalmic features of Graves' disease, a goitre, or neurosis. Any of these may have had subclinical hyperthyroidism which only this test could recognize; but in some a hyperplastic goitre, without even subclinical hyperthyroidism, may have been the basis of the test results. Although the confirmed hyperthyroid group included some very mild cases, clearly some patients with minor or transient signs of hyperthyroidism will have escaped confirmation and so be found in the group with 'hyperthyroidism not confirmed'.

We conclude that a normal thyroid uptake should exclude hyperthyroidism, if previous iodide or drug administration can also be excluded; that a 'probably high' uptake implies a hyperplastic goitre with or without subclinical hyperthyroidism; and that a 'high' uptake is usually (80 per cent. of cases) accompanied by clinically confirmable hyperthyroidism, while in the remaining cases either the thyrotoxicosis is too mild for certain clinical confirmation, or only a hyperplastic goitre is suggested.

2. *Patients provisionally diagnosed as having non-toxic goitre* (49 tests; Fig. 6). These patients were seen because of a goitre which at the time of the initial urinary test was thought to be functioning normally; the urinary test results are shown in Fig. 6, grouped according to the final clinical diagnosis. The final diagnosis of the type of goitre was based on the clinical examination, supported in some cases by studies of the distribution of radioiodine uptake in the gland, and in most cases by the appearance and histology of the gland at operation. Studies of the distribution of radioiodine uptake in the gland permitted classification of eight solitary nodules, as 'hot' where most of the radioactivity was concentrated in the nodule, or 'cold' where the opposite was the case. In none of these patients has thyroid cancer been found, and no tests made on patients with the initial diagnosis of thyroid cancer have been analysed in the present series, excepting two patients who had functioning metastases. None of these 49 patients was later found to have hyperthyroidism, and only one, who had a goitre with myxoedema, was later proved to have had hypothyroidism. The major diagnosis of non-toxic goitre has been confirmed in 43 cases, that is, in all except the last three sub-groups (chronic thyroiditis, goitre with myxoedema,

and non-thyroid tumours). The test results were normal in 34 (79 per cent.) of these cases, 'low' or 'very low' in five, and 'high' or 'probably high' in four. The 'high' and 'probably high' results were found among the nodular goitres; with two of the three 'hot' solitary nodules the results were 'high'. The 'low' and 'very low' values were scattered through all the sub-groups, but included two of the five 'cold' solitary nodules; the other three 'cold' solitary nodules were at the lowest limit of the normal range. A final diagnosis of chronic thyroiditis (lymphadenoid goitre) was made histologically in three of these patients; two had shown a normal and one a 'high' uptake. Another patient, also finally diagnosed as having chronic thyroiditis (lymphadenoid goitre), had shown a low normal thyroid uptake by the urinary test; she was confirmed as having mild myxoedema, under which diagnosis her result appears. The patient who had 'goitre with myxoedema' had received thyroid for 20 years until three years before the test, and probably had myxoedema at the time of the test, as thyroid was later necessary to relieve the signs of myxoedema. Her urinary test showed a 'very low' uptake. Of the two patients with non-thyroid tumours (lymphangioma and cervical adenitis) one certainly, and the other probably, had had iodides, to which their low uptakes may be due.

In summary, patients with non-toxic goitre had normal uptakes in 79 per cent. of tests in which this diagnosis was confirmed. About 10 per cent. showed lowered uptakes, but none of these patients developed post-operative myxoedema, so that iodides cannot be excluded as a cause of their test results. Another 10 per cent., who evidently had hyperplastic goitres with or without subclinical hyperthyroidism, showed 'probably high' or 'high' uptakes. This is a lower proportion of such raised uptakes than that found (25 of 72) in the two sub-groups of the preceding section, in which the final diagnosis was also non-toxic goitre, though the patients were originally suspected of hyperthyroidism. We conclude that this test can confirm most non-toxic goitres as being non-toxic, but will show that some of them have lowered or raised uptakes; the latter are hyperplastic glands, but whether they are also over-secreting cannot easily be determined with finality by present clinical methods. No test result was found to be characteristic of the four lymphadenoid goitres studied.

3. *Patients suspected of hypothyroidism or myxoedema* (59 tests; Figs. 5 and 6). During the clinical observation of four of these patients myxoedema was not only confirmed, but its origin was traced to chronic absorption of resorcinol applied to leg ulcers; fuller studies of these patients, and of the antithyroid action of resorcinol, have been reported elsewhere (Bull and Fraser, 1950). On their initial admission to hospital, immediately after the accidental withdrawal of goitrogen, all these patients showed by the urinary test the high thyroid uptakes (Fig. 5) typical of recent prolonged antithyroid drug administration. Myxoedema was confirmed in 28 other patients (32 tests), and the test results are shown in Fig. 5. Of these 32 tests, T values were 'very low' or 'low' in 28 (24 and four respectively); the other four values were in the normal range, though well below the normal mean. As we have already remarked, the use of the k_t index hardly alters these interpretations, except that it classes one of the four

normal values as 'very low', and brings the division between 'low' and 'very low' gradings more into accord with the severe and mild clinical sub-groupings. Interpretation by the 8-24-hour excretion would class two less (26) of these tests as subnormal. The three patients who gave normal test results by both T and k_t criteria undoubtedly had myxoedema. One test was suspected of an error of collection, but could not be repeated. One of the other patients, a boy of 11 years, had typical infantile myxoedema, which responded strikingly to thyroid treatment; 5 per cent. of his dose of radioiodine was present in the neck at 56 hours, with a neck/thigh ratio of 4.0. The third patient, an obese woman with a goitre and some signs of myxoedema, had a basal metabolic rate of -22 per cent., plasma-cholesterol 410 mg. per 100 ml., typical electrocardiographic changes, and a lymphadenoid goitre on biopsy; her symptoms were mild, but responded to treatment with thyroid. Evidently low normal values do not exclude myxoedema in a few cases. The results were normal in the remaining patients, in whom myxoedema could not be confirmed clinically; alternative diagnoses of heart disease, psychoneurosis, or other endocrine disease were made. Minor degrees of myxoedema are hard to exclude clinically; and most of the uptakes in these patients were below the normal mean. It is of interest to note that in four patients who had Simmonds's disease, without obvious clinical evidence of myxoedema, this urinary test result was normal. This fact probably reflects the insensitivity of the test to minor thyroid defects, and is an important limitation to remember in assessing pituitary defects. The result is in contrast to the findings in four other patients who had Simmonds's disease with obvious clinical signs of myxoedema; their results have been included in the group of confirmed myxoedema, and were typically abnormal.

4. *Tests made in other thyroid disorders* (Fig. 6). (1) *Subacute thyroiditis*. One patient with typical signs of subacute thyroiditis was tested in the present series, and two others in the subsequent year's series. The uptake of radioiodine was absent or insignificant in all three cases, but returned to normal after remission of the disease. These three cases, with their full test results, have been reported in detail elsewhere (Fraser and Harrison, 1952). The basal metabolic rate, plasma-cholesterol, and protein-bound iodine were all found to be normal throughout the course of the disease. (2) *Functioning metastases from thyroid carcinoma*. In two such patients radioiodine uptake was demonstrated in the lungs. By the urinary data one showed a normal total uptake, which accorded with her euthyroid status, and the other a 'high' thyroid uptake, which accorded with the clinical signs of associated thyrotoxicosis; these signs subsided after radioiodine therapy.

Discussion

Several previous publications (McArthur, Rawson, Fluharty, and Means, 1948; Skanse, 1949; Keating, Haines, Power, and Williams, 1950; Goodwin, Macgregor, Miller, and Wayne, 1951), as well as our analysis, have indicated the limited diagnostic value of the total urinary radioiodine excretion in 0 to 24 and 0 to 48 hours. This test is particularly liable to fail in the recognition of

hypothyroidism, in which some renal impairment is usual, and the total urinary excretion consequently often normal. Our suggested procedure can overcome both this limitation and the main general objections to urinary excretion tests; by subdividing the urinary collections, one can incorporate both a check on error and an interpretation by indices of thyroid uptake which are relatively independent of renal function. Other authors have found an advantage in subdividing the urinary collection (Keating, Power, Berkson, and Haines, 1947; Marinelli, Quimby, and Hine, 1948; Skanse, 1949; Mason and Oliver, 1949). Both the above devices, which this subdivision permits, are probably essential for a clinically reliable urinary radioiodine test, and they still leave this test possibly the simplest to perform with radioiodine and the one needing least radioactivity. From our analysis this type of urinary radioiodine test of thyroid function emerges as reasonably reliable and clinically useful within certain defined limits. We have not examined the question whether other radioiodine tests give more specific and sensitive indices of thyroid function. Keating, Haines, Power, and Williams (1950) found a comparable type of urinary test, measuring also the extrarenal disposal rate, to be as sensitive a measure of hyperthyroidism or hypothyroidism as either of the non-urinary methods with which they compared it—the *in vivo* 24-hour thyroid accumulation, and the thyroid accumulation rate. It is probable that the diagnostic limitations of a suitably designed urinary excretion test are those inherent in the use of thyroid uptake as an index of thyroid function; this consideration would therefore apply to the methods of testing *in vivo* thyroid clearance and uptake rate given by Pochin (1950), Foote and MacLagan (1951), and Reiss, Hemphill, Maggs, Smith, Haigh, and Reiss (1951). The possibility of a preceding administration of iodides, thyroid, or antithyroid drugs must always be remembered as a likely cause of abnormal results with any radioiodine test. Goodwin, Macgregor, Miller, and Wayne (1951) have proposed the measurement of the 48-hour plasma-protein-bound radioiodine for the more specific recognition of hyperthyroidism; but while it was only very slightly more specific than their clearance-rate measurements in hyperthyroid patients, it did not recognize two of 26 of their confirmed thyrotoxic patients, and it is not applicable to the recognition of myxoedema, for which improved sensitivity is most required.

The normal range of thyroid uptake has been adequately defined for our area; its value is slightly higher than that defined by Keating, Haines, Power, and Williams (1950) for Minnesota (0-48-hour urinary excretion higher, and k_t values lower), slightly lower than that defined for Sheffield by Goodwin, Macgregor, Miller, and Wayne (1951), and considerably lower than that found by Stanbury, Brownell, Riggs, Perinetti, del Castillo, and Itoiz (1952) in an iodine-deficient area of Argentina. Clearly the normal and abnormal ranges must be defined for each area in which the test is used, and the test will be less sensitive to myxoedema in areas with lower ranges of normal thyroid uptake. We have found that the test can recognize five clinically useful grades of thyroid uptake—'high', 'probably high', normal, 'low', and 'very low'. The 'high' uptake range, defined from a group of confirmed thyrotoxic cases, is fortunately separated

from the normal range by a 'probably high' grade, which therefore can signify either a simple hyperplastic thyroid or subclinical hyperthyroidism. Either 'low' or 'very low' uptake can confirm myxoedema. Clearly abnormal uptake will not always imply abnormal secretion, though this may develop later; among 43 non-toxic goitres without any clinical hint of abnormal function, 20 per cent. showed abnormal uptakes, which were about equally divided between raised and lowered values. Evaluation of any test of thyroid function must be against the clinical assessment, which cannot be precise. To make our appraisal as reliable as practicable we have made it against a final diagnosis made six or more months after the test, so that the response to therapy could contribute to its accuracy, and dubious or purely symptomatic responses have not been accepted. While this has left a few mild instances outside the groups of confirmed thyroid disorder, it must be repeated that these groups included many clinically mild cases; of the confirmed cases of thyrotoxicosis, only about a quarter were clinically obvious initially.

As has been found with all other radioactive iodine tests, the test we have described is more sensitive to thyrotoxicosis than to myxoedema. All untreated and clinically confirmed thyrotoxic patients showed 'high' thyroid uptakes, while only 28 of the 32 tests of patients with confirmed myxoedema showed either 'low' or 'very low' thyroid uptakes. The test can help to exclude a suspicion of thyrotoxicosis; 80 per cent. of our patients with suspected but unconfirmed thyrotoxicosis gave normal results. We have not confirmed the finding by Keating, Haines, Power, and Williams (1950) of normal results in some instances of thyrotoxicosis, especially adenomatous hyperplastic goitres; possibly because our requirements for the clinical confirmation of thyrotoxicosis were more stringent. On the other hand, like other investigators, we have found 'high' uptakes in suspected but unconfirmed hyperthyroidism (19 cases out of 138) finally diagnosed as non-toxic goitre, ophthalmic Graves' disease, or neurosis, as well as in a few cases (3 out of 43) of apparently simple non-toxic goitre and in drug myxoedema. The basis of the high uptake in these patients who had unconfirmed suspected thyrotoxicosis may often have been subclinical hyperthyroidism, for all had shown some of the features of Graves' disease in the form of goitre, eye signs, or nervousness. Thus there were fewer really 'false' high uptakes, and some of these patients would probably later become hyperthyroid; little harm might have resulted if they had all been treated as hyperthyroid. The proportion of patients who had unconfirmable thyrotoxicosis with a 'high' uptake corresponds to the proportion of confirmed thyrotoxic patients not recognized by Goodwin, Macgregor, Miller, and Wayne (1951) by estimating the 48-hour protein-bound ^{131}I . It is generally agreed that some patients with confirmed myxoedema show a normal percentage uptake of radioiodine by the thyroid. Keating, Haines, Power, and Williams (1950) found that one-third of such cases overlapped into their normal range. Their normal range allowed less room for further lowering than ours (k_t from 2.1 to 7.3 per cent. compared with 4.4 to 11 per cent.). This difference in the normal range may also be the reason why we have not found a lowered uptake without either thyroid disease or

clinically severe renal disease. Among 14 non-uraemic renal patients, only three with obvious severe renal disease showed 'low' or 'very low' uptakes by both k_t and T indexes, and none of our nine patients with heart failure did so. Like other investigators, we have found lowered thyroid uptakes with subacute thyroiditis, though not with all our few lymphadenoid goitres; lowered uptakes were also found in a few cases of non-toxic goitre, in which, however, previous administration of iodides could not be excluded as the cause.

APPENDIX

A qualitative test for excess of urinary iodide. To a pair of test-tubes add 0.2 ml. and 1 ml. from the 24-48-hour collection of urine made up to 2 litres; standard tubes should also be used with, instead, water and 0.1 ml. of a solution of iodide (0.5 mg. I per litre). To each tube then add also: 5 ml. water, 1 ml. arsenious acid solution (0.075 N arsenious acid in 0.75 N H_2SO_4 and 0.5 per cent. NaOH), and finally, in quick sequence along the tubes, 0.4 ml. ceric sulphate (0.1 N ceric ammonium sulphate in 3.5 N H_2SO_4). The result is read at half an hour; no fading of the yellow colour in either tube shows less than 0.1 mg. I per 24 hours, and complete fading in both more than 0.5 mg. I per 24 hours.

Summary

1. A simple technique for testing thyroid function by urinary radioiodine excretion is described. Urine is collected in three periods, from measurements of which three indices of thyroid uptake can be derived—a T index, the 8-24-hour excretion, and a k_t index.

2. The efficiency of these indices has been compared by means of groups of normal subjects and patients with confirmed primary renal disease, primary cardiac disease, hyperthyroidism, and hypothyroidism. The result has suggested the following method of using the indices. The T index is used as a routine, and compared usually with the 8-24-hour excretion in order to check for errors of collection; when a low thyroid uptake is found, or renal disease is evident, this check should be made with the k_t index instead.

3. In the Appendix a simple chemical test for urinary iodide is described which should reveal recent iodide administration.

4. Tests of 23 patients with renal disease have shown the three indices to be sufficiently independent of renal function for clinical use.

5. The clinical usefulness of the test has been assessed from 397 test results compared with the final diagnosis made six months after the test:

(a) The test is more sensitive to hyperthyroidism than to hypothyroidism, and all confirmed hyperthyroid cases (83 tests) showed a 'high' thyroid uptake.

(b) Among 138 patients with suspected but unconfirmed hyperthyroidism, 89 showed a normal thyroid uptake, but 19 'high' uptakes were also found in non-toxic goitre, ophthalmic Graves' disease, and a few cases of neurosis.

(c) Among 43 patients with confirmed non-toxic goitre, 34 showed a normal thyroid uptake; 'high' uptakes occurred among nodular goitres, especially 'hot' solitary nodules.

(d) Among 32 tests of patients with confirmed myxoedema, 28 tests showed a 'low' or 'very low' thyroid uptake, but three showed low normal uptakes. 'Low' and 'very low' uptakes were also found in subacute thyroiditis, and occasionally in non-toxic goitres.

(e) Four patients with myxoedema due to drugs showed a 'high' thyroid uptake.

(f) Among 23 patients with unconfirmed myxoedema the test results were all normal. Four of these patients had Simmonds's disease without clinical myxoedema.

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THE FACTOR OF INFECTION IN CHRONIC BRONCHITIS¹

By C. H. STUART-HARRIS, MARGARET POWNALL,
CYNTHIA M. SCOTHORNE, AND ZENA FRANKS

(From the Department of Medicine, University of Sheffield)

THE subject of infection as a factor in the aetiology and course of chronic bronchitis is a much neglected one. This is probably due partly to a feeling that such a chronic disease is degenerative rather than infective in origin, and partly to past inability to interfere with the course of an infection in a specific manner. The introduction of the antibiotics has, however, now made it possible to alter the symptoms of chronic bronchitis, and the factor of infection has therefore become important. It is the purpose of the present communication to examine the evidence of its mode of action as critically as possible.

The Normal Flora of the Respiratory Tract

Contrary to earlier beliefs, the portion of the respiratory tract below the larynx is not swarming with bacteria, but maintains in health a considerable degree of freedom from pathogenic organisms. This is more remarkable when one remembers the demonstration that, in sleep, nasopharyngeal secretions contaminated with bacteria can enter the bronchus. Yet, if swabs are taken of the mucosa about the level of the bifurcation of the trachea, or even below it, by means of a bronchoscope or some similar method, cultures in health are either sterile or at the most yield only a few colonies of nasopharyngeal organisms. Examination of the trachea soon after death, even if the latter occurs suddenly, does however yield organisms, and this fact can be explained either by post-mortem seepage of secretion or, as Smillie and Duerschner (1947) thought, by agonal extension of nasopharyngeal secretions. Observations indicate, therefore, that little information of value concerning bronchial infection can be obtained by post-mortem studies. Moreover, though the lungs are usually sterile either in health or after sudden death, it is not the alveoli which are of special interest in connexion with the subject of chronic bronchitis. In order to explain the sterility of the trachea and bronchi in health there must be a constant process of surface-disinfection, probably by the upward-moving sheet of respiratory mucus which is propelled by cilia, to which are added leucocytes derived by diapedesis between the epithelial cells. The efficacy of such a process clearly depends in part upon mechanical factors, and also upon circumstances such as temperature and humidity which modify ciliary action.

Above the larynx, the posterior nasopharynx maintains a state of constant saprophytism, with a tolerance towards certain organisms of a potentially

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invasive character. It is generally agreed that cocci of the Gram-negative catarrhalis family, non-haemolytic and green-producing streptococci, diphtheroids, rough species of the haemophilus family, and non-coagulase-producing staphylococci, are constant dwellers in the nasopharynx. But pneumococci of many types, haemolytic streptococci, and *Bact. friedländeri* are also found in the nasopharynx in numbers which vary greatly in normal individuals, at

TABLE I
Nasopharyngeal Carrier Rates in Adults (Single Swabbings)

Species	Carriers (%)	
	Nasopharynx	Nose
Pneumococci	20-40	5-15
Haemolytic streptococci	5-15	Uncommon
<i>H. influenzae</i>	40-80	5-10
<i>Staph. pyogenes</i>	?	40-50*
<i>Bact. friedländeri</i>	1-8	?

After Straker, Hill, and Lovell (1939).
* Miles, Williams, and Clayton-Cooper (1944).

different seasons and under different conditions, in an apparently random fashion. A less intensive colonization with pneumococci and *Haemophilus influenzae* is present in the nose, which, however, is the special province of the *Staphylococcus pyogenes*. Carrier-rates usually quoted are based upon single swabbings of different individuals, and Table I, taken from Straker, Hill, and Lovell (1939), indicates the typical findings in adults. It is important to realize that repeated swabbings of normal individuals increase the apparent frequency with which the different species of organisms are found, and it is clear that all these bacteria are in a constant state of flux, and that any one person acts as a carrier of every species at one time or another. Some species such as the pneumococcus, in which individual types are readily distinguished, can be divided into types commonly present in normal throats—such as Types III, VI, and many of the higher types—and others such as Types I, II, and V, which are uncommon in normal persons, but which are frequently found in the sputum of patients with pneumonia. The question of carriage of viruses in the normal throat is still far from settled. It is not generally believed that the influenza viruses reside in latent form in normal subjects except during epidemics. But no one can deny the possibility, indeed probability, that viruses such as that of the common cold may in fact persist in normal subjects without producing clinical signs.

The work of Straker, Hill, and Lovell (1939) and of Rosher (1939) on the extension of the nasopharyngeal flora, and particularly of pneumococci and *Haemophilus influenzae*, up into the nose, and perhaps downwards into the trachea, during colds or at certain seasons of the year (Table II), has received less notice than it deserves. It cannot be denied that acute virus infections of the respiratory tract probably disturb distribution, as well as the quantitative relationships, of the bacterial flora. Thus, even if respiratory epidemics cause no general increase of bacteria carried in the nasopharynx, they

probably influence the normal relationships of a host to his own flora, and sometimes they do so to the host's detriment. It is particularly necessary to stress the mechanical disturbance also produced by viruses such as the influenza virus, which parasitize epithelial cells, in the normal defence mechanism of the lower respiratory tract. It is still not known whether the increased flow of mucus during infection is a form of defence against viruses, or a symptom

TABLE II
Seasonal Incidence of *H. influenzae*

Time of year	% of Subjects		
	Nasopharynx	Trachea	Nose
1st quarter . .	66.9	39	9.8
2nd " . .	64.7	23	8.0
3rd " . .	60.5	19	3.8
4th " . .	61.3	24	4.3

After Rosher (1939).

of a failure to limit infection, but any factor which increases the exudation of fluid into the lower respiratory tract is likely to aid the bacteria rather than the host.

Bacteriological Findings in Chronic Bronchitis

Examination of the sputum, or of material obtained by bronchoscopic aspiration, during the various phases of ill health in chronic bronchitis does not reveal a constant flora. Allison, Gordon, and Zinnemann (1943) reported that, among a group of 26 cases of chronic non-purulent bronchitis investigated by bronchial aspiration, 14 specimens were sterile, and 12 yielded a variety of organisms not including *Haemophilus influenzae*. In contrast, among 100 cases of bronchiectasis similarly investigated, only seven specimens were sterile, and 63 yielded *Haemophilus influenzae*. Benstead (1950) also found seven of 11 specimens from the bronchial tree of patients with tracheitis and bronchitis associated with emphysema to be sterile. Mulder of Leiden emphasized in his own studies (1938) the specially close relationship between *Haemophilus influenzae* and chronic bronchitis, and did not draw any clear-cut distinction between the parts played by it in bronchitis and in bronchiectasis. Both the Leeds workers and Mulder used media which favoured the growth of haemophilus organisms, and there is little doubt that considerable experience is necessary before reliable observations can be made regarding the frequency of these organisms in particular specimens.

Because of the prolonged duration of chronic bronchitis, it is necessary to consider the bacteriological findings obtained in relation to the several phases of the condition. These are first the initial phase, which may be a definite event or a more ill-defined stage lasting for some years, and secondly the phase of chronic ill health, during which the patient is aware of a productive cough and a greater or lesser degree of dyspnoea, but is able to work and maintain a reasonably normal existence. The sputum may or may not be purulent. This period is broken by acute illnesses, chiefly in winter-time, accompanied

by increased cough, a purulent sputum, and increased dyspnoea, until there comes the terminal phase of pulmonary insufficiency or of congestive heart failure, which is again punctuated by periodic exacerbations until the final event. It is rarely possible to study the initiating phases of chronic bronchitis, nor is retrospective inquiry often fruitful. An inquiry as to the time from which a patient dates his chronic illness sometimes elicits the history that it followed an attack of pneumonia, or an unusually severe attack of influenza, especially in men aged 50 years or over with a relatively short history of bronchitis. In other patients, with a long history dating back to childhood, there is rarely any specific illness which is remembered. Those who served in the First World War often say that they blame gassing for the initiating circumstance. On the whole, therefore, there is nothing to indicate that infection of the respiratory tract is a specific provoking cause of the subsequent chronic process. Observations have been made by us in Sheffield during the period 1948 to 1952, with particular reference to the pneumococcus and the influenza viruses in the acute exacerbations suffered by patients with chronic bronchitis with or without heart failure. Recently patients with chronic bronchitis admitted primarily for investigation have been included, but the bacteriology of the sputum has again been studied chiefly from the standpoint of the pneumococcus. No attempt has been made specifically to assess the role of *Haemophilus influenzae*.

Methods

Sputum was cultivated as a routine on blood agar, and the dominant organisms were identified. *Haemophilus influenzae* was noted only when present in large numbers. Haemolytic streptococci and coagulase-positive staphylococci were noted when present. Gram-negative cocci, diphtheroids, and the non-haemolytic and green streptococci were ignored. In many instances sputum was emulsified and injected intraperitoneally in mice. Typing of pneumococci thus obtained was carried out with the aid of typing sera obtained from the State Serum Institute, Copenhagen. Tests for influenza-virus infection included attempted isolation of virus by means of inoculation of sputum emulsion into 13-day-old fertile hens' eggs. Serological methods included complement-fixation tests and the agglutination-inhibition test, with antigens prepared from the PR8 or W.S. influenza A viruses and the Lee strain of influenza virus B. At least a fourfold increase in titre between the serum taken on admission to hospital and that obtained 14 days later was required as significant evidence of influenza-virus infection. The presence of a high titre of antibody by the complement-fixation reaction in the first serum, if it was maintained or fell during further observation, was regarded as suggestive evidence of recent infection by the virus concerned (post-influenza state).

Results

Table III shows the clinical material to which the bacteriological results apply. There were 113 patients, 90 men and 23 women. Cases of pneumoconiosis, tuberculosis, and gross bronchiectasis have been excluded. The peak

in age was 50 to 60 years, but many of the subjects were under 50 years old. All but 28 of the patients were admitted to hospital primarily for treatment; the seasons at which exacerbations required admission are shown by consider-

TABLE III
Patients Investigated

	Number of patients	Sex	Age (years)						
			M	F	30– 39	40– 49	50– 59	60– 69	70 or over
Chronic bronchitis	28	23	5		2	6	10	10	0
Chronic bronchitis with ex- acerbation	50	36	14		1	5	19	22	3
Congestive heart failure	35	31	4		2	7	19	7	0
Totals	113	90	23		5	18	48	39	3

ing admissions month by month. Fig. 1 shows the monthly admissions of the 50 patients with chronic bronchitis in acute exacerbation, and of the 35 patients with heart failure in addition, many of whom were admitted on several occasions. The preponderance of winter attacks is striking, and though the cases

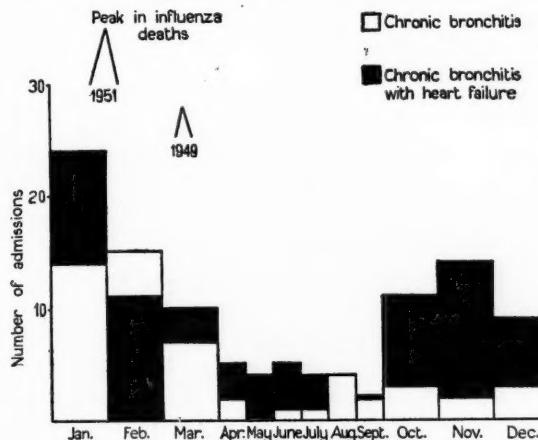


FIG. 1. Chronic bronchitis: seasonal trend in admissions to hospital in 1948–52.

without heart failure were grouped largely in the first quarter of the year during the influenza seasons, those with heart failure sought admission both before and after Christmas, and showed less tendency to be grouped in relation to epidemics. The period of study included two epidemics of influenza A, one having its peak in March 1949 and the other in January and February 1951. Table IV shows the results of cultivation of the sputum in cases of chronic bronchitis with or without acute exacerbation, but excluding patients with heart failure. The figures must be regarded as minimum figures only. If mouse-inoculation of the sputum is practised, the frequency of recovery of the

pneumococcus rises considerably, and routine investigation of the sputum by this method was utilized only in the case of patients admitted in 1951 and 1952. As selective media were not employed, it is quite certain that haemophilus organisms were often missed. But it is clear that the staphylococcus and haemolytic streptococcus were unimportant inhabitants of the sputum. Figures for *N. catarrhalis* and for non-haemolytic and green-producing streptococci are not given because of the ubiquity of these organisms. Tests for influenza-virus

TABLE IV
Bacteriology of the Sputum in Chronic Bronchitis

	Number of patients	Sputum cultures			
		Pneumo- coccus	<i>H. in- fluenzae</i>	Haemolytic strepto- coccus	Staph. pyogenes
Chronic bronchitis (relative quiescence)	28	15	5	1	0
Chronic bronchitis (acute exacerbation)	50	23	7	2	6 (Coliform bacilli 2)

Tests for influenza virus infection

	Number tested	Positive*	Negative
Chronic bronchitis (relative quiescence)	6	1 (post-influenzal)	5
Chronic bronchitis (acute exacerbation)	23	15 virus recovered serum positive post-influenzal	4 5 6

* All instances of influenza A.

infection were carried out chiefly during periods of exacerbation. The influenza virus A was frequently a cause of clinical relapse of a severity necessitating admission to hospital. Of course many minor relapses, treated at home, occur in such patients, and are often attributed by them to weather or to colds. The impossibility of making laboratory tests with the common-cold virus has prevented any observations on this virus as a precipitating cause of relapse.

The clinical signs of infection of the respiratory tract during acute exacerbations are not prominent. Fever may be present, but is usually slight. There is, however, increased cough and dyspnoea, and the sputum is purulent and sometimes blood-streaked. The anatomical process is presumably an acute bronchitis or bronchiolitis. Another infection which occurs frequently in patients with chronic bronchitis is pneumonia. So many of the adult patients with lobar or segmental pneumonia admitted to hospital in Sheffield give a history of chronic cough or sputum as an antecedent to their acute disease, that it is hard to believe in the existence of primary pneumonia in adults. Thus out of a series of 111 patients with clinical and radiological evidence of consolidation, admitted to hospital during 1950-1, 42 gave a history suggesting pre-existing chronic bronchitis. The bacteriological findings in cases of pneumonia are not the same as those in chronic bronchitis without consolidation of the lungs, as will be

shown later. But the pneumococcus is certainly the most important bacterium concerned in causing consolidation either with or without a chronic history, and the evidence favours the view that the infection is in both cases an exogenous one, derived from some other individual.

Chronic bronchitis with congestive heart failure. Table V shows the bacteriological results obtained in cases of chronic bronchitis with congestive heart failure. Many of the 35 subjects were studied in successive relapses of failure,

TABLE V
Bacteriology in Cases of Chronic Bronchitis and Emphysema with Congestive Heart Failure

Number of patients	Number of exacerbations	Sputum cultures				
		Pneumo-coccus	H. influenzae	Haemolytic streptococcus	Staph. pyogenes	Bact. friedländeri
35	94	49	14	5	14	2
(Coliform bacilli, 3)						
<i>Tests for influenza virus</i>						
Number of patients	Number of exacerbations tested	Positive			Negative	
		4 { serum positive 3			16	
18	20	post-influenza 1				

TABLE VI
Out-Patients Tested Periodically for Influenza-Virus Infection in the Winter of 1950-1

	Number of patients	Increase of influenza A antibody	
		Positive	Always negative
Chronic bronchitis	8	2	6
Chronic bronchitis with heart failure	14	4	10
Total	22	6	16

and 94 such relapses were examined. The findings did not differ greatly from those obtained in chronic bronchitis without heart failure. The pneumococcus was again important. *Staphylococcus pyogenes* was apparently more important than in chronic bronchitis, perhaps because of the frequent attendance of these patients at hospital. The influenza viruses seemed less often to cause clinical relapse in this group of patients, and this point was also brought out by routine serological study in an out-patient clinic, during the winter of 1950-1, before and after an epidemic of influenza A (Table VI). Sixteen of 22 subjects showed no serological evidence of infection, though subclinical infection, proved serologically, was common in the community during the outbreak. Of the six patients who developed serological evidence of influenza during the period, only three had experienced clinical signs of the infection. Subclinical infection by the virus may therefore occur in cases of chronic respiratory disease, as in

normal subjects. Conversely, during the recent winter (1951-2), though epidemics of respiratory disease have not occurred, frequent relapses of congestive failure have occurred in patients with chronic bronchitis and emphysema; the common cold was usually blamed by these patients for their relapse. The clinical signs of infection of the respiratory tract in these relapses are not im-

TABLE VII
Repetition of Cultures of Sputum in Cor Pulmonale

C. J., Male, aged 39 years. Symptoms for 14 years

Attack of congestive heart failure	Date	Pneumococcus		H. in- fluenzae	Haemolytic strepto- coccus	Staph. pyogenes
		±	Type			
1st . . .	July 1949	+	..	-	+	-
2nd . . .	Nov. "	+	..	-	-	-
3rd . . .	Nov. 1950	+	XI	-	-	-
4th (with pneu- monia)	{ Jan. 1951 Feb. "	+	I	-	-	-
5th . . .	Apr. "	+	..	+	Coliform bacilli	-
Minor operation .	July "	-	..	+	-	-
6th . . .	Oct. "	-	..	-	-	-
7th . . .	Jan. 1952	+	..	-	-	-
8th . . .	Mar. "	+	XIV	-	-	-

H. D., Male, aged 39 years. Symptoms for 10 years

Attack of congestive heart failure	Date	Pneumococcus		H. in- fluenzae	Haemolytic strepto- coccus	Staph. pyogenes
		±	Type			
1st . . .	Feb. 1950	{	+	-	-	+
2nd . . .	Dec. "	+	-	-	+	+
3rd (with pneu- monia)	Jan. 1951	-	-	-	-	+
4th . . .	Nov. "	-	-	-	-	+
5th (Died) . . .	Jan. 1952	+	-	-	-	-

pressive. Fever is usually absent, but there is increased sputum and cough, as in exacerbations of chronic bronchitis without congestive failure. Only three of the relapses in patients with heart failure were associated with frank consolidation of the lungs. Bacteriologically two of these cases were pneumococcal in origin, and the third seemed to be due to *Staphylococcus pyogenes*. The pertinacity with which the sputum is colonized by bacteria in cases of chronic bronchitis with heart failure can best be visualized by reference to Table VII, which details the findings in two patients who were admitted on numerous occasions.

Significance of the Bacteriological Results

The presence of bacteria in the sputum of cases of chronic bronchitis can mean one of three things. First, there may be a state of saprophytism in the lower respiratory tract. Secondly, the bacteria may be producing a state of infection, and may have been derived from a source external to the patient (exogenous infection). Thirdly, the bacteria may be producing a state of infection, but may be derived from the upper respiratory tract of the same individual (autogenous infection). In order to decide which of these possibilities

is correct, it is of interest to compare the findings with those in pneumonia and in bronchiectasis. The organisms found in the sputum of patients in pneumonia and bronchiectasis are usually regarded as being concerned in producing a true infection, in the one case of the alveoli and in the other of the walls of the dilated bronchi. Table VIII shows, for comparison with the findings in chronic bronchitis, the results obtained in Sheffield from patients with pneumonia of

TABLE VIII
*Comparison of Organisms in the Sputum in Cases of Pneumonia,
Bronchiectasis, and Chronic Bronchitis*

Category	Number of specimens	Pneumo-coccus	H. influenzae	Haemolytic strepto-coccus	Staph. pyogenes	Bact. friedländeri
Pneumonia, 1947-51	296	218	..	5	40	3
296 cases	..	(73·6%)	..	(1·7%)	(13·5%)	(1·0%)
Chronic bronchitis (all phases), 1948-52	172	87	26	8	20	2
113 cases	..	(50·5%)	(15·0%)	(4·6%)	(11·6%)	(1·1%)
Bronchiectasis, 1949-52	45	26	10	2	7	2
27 cases	..	(58·0%)	(22·2%)	(4·4%)	(15·5%)	(4·4%)

TABLE IX
Types of Pneumococci

Clinical category	Strains investigated and typed	Pneumococcus types		
		I-VIII	IX-XXI	XXII-XXXVI
Pneumonia (Sheffield) 1947-51	224	172	30	22
		(76·7%)	(13·3%)	(9·8%)
Chronic bronchitis (all categories) 1948-52	42	11	20	11
		(26%)	(47·6%)	(26%)
Normal carriers (nasopharynx) (Straker, Hill, and Lovell, 1939).	..	40·2%	34·7%	25·1%

Percentage incidence of certain types

	Pneumonia	Chronic bronchitis	Normal carriers
Types I and II	25·2	2·4	1·4
Type III	20·5	12·1	20·40
Type XIX	3·1	19·0	1·2

all varieties, and from patients with gross bronchiectasis admitted to hospital in relapse but not with pneumonic consolidation. In all three clinical groups pneumococci, *Haemophilus influenzae*, and *Staphylococcus pyogenes* are important. The differences between the flora in cases of bronchiectasis and that in cases of chronic bronchitis are slight. *Haemophilus*, if found, was usually present in greater abundance, and was often mouse-virulent, in the cases of bronchiectasis. Pneumococci would have been found in a higher percentage if mouse-inoculation had been practised as a routine. Further information can

be obtained by identifying the serological species of organisms, and this procedure is most practicable with pneumococci and *Staphylococcus pyogenes*. It is not possible with rough haemophilus species. Table IX shows the type-distribution of pneumococci obtained in cases of pneumonia and chronic bronchitis. Typing was pursued in cases of bronchitis mainly during 1951 and 1952. Seventy-six per cent. of the types of pneumococci in cases of pneumonia belonged

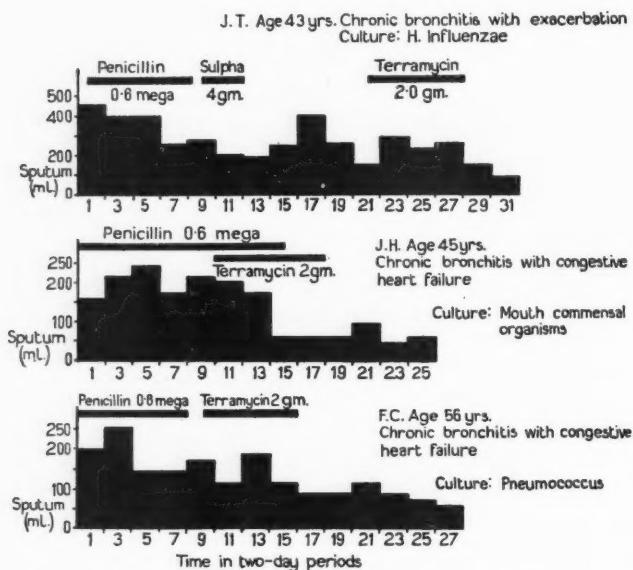


FIG. 2. The effect on sputum of treatment with antibiotics.

to Types I to VIII, and Types I and II comprised no less than 36 per cent. But in chronic bronchitis the distribution was spread throughout the range, Types XIX, XXII, and III being in excess of the other types. The findings are not exactly the same as in the normal nasopharynx, where types such as III, VI, and XXVI have been preponderant in published series. Types I and II are present in the normal nasopharynx in less than 3 per cent. of persons, and in such a high proportion of cases of pneumonia as to lead to the assumption that infection is exogenous in that disease. On this line of reasoning, the pneumococci in chronic bronchitis may well be derived autogenously from the patient's own throat.

The resemblance between the flora in bronchitis and that in bronchiectasis, where there are gross anatomical lesions, is important. Analogy exists with the presence of bacteria in skin lesions or in wounds, in which it is often difficult to tell precisely what the bacteria are doing. Healing of the skin or of wounds, for instance, will ultimately occur in spite of a rich bacterial flora. Yet careful studies have shown beyond doubt that healing is delayed if bacteria such as staphylococci and haemolytic streptococci are present in wounds (Miles, 1944).

Elimination of the organism is the only safe method of deciding whether or not its presence is harmful. In the case of chronic bronchitis the organisms are eliminated from the sputum with varying degrees of ease by antibiotic treatment. Sensitivity of the organism to the antibiotic, ability to build an effective concentration of antibiotic in the surface secretions, and tendency to relapse or superinfection with fungi or coliform organisms, are the most important factors governing success or failure. Penicillin is highly effective against the pneumococcus, but somewhat less effective against haemophilus. Its use in chronic bronchitis is accompanied by a lessening of cough and a diminution in the purulent character of the sputum, though it is rare in our experience for the sputum to dry up. The various antibiotics of the streptomycetes family are more regularly inhibitory to haemophilus. We have personal experience chiefly of terramycin, and have found that its use is frequently accompanied by a further diminution in the amount of sputum, even after the use of penicillin (Fig. 2). An extensive trial of antibiotics by Mulder, Goslings, van der Plas, and Cardozo (1952) at Leiden suggested that elimination of haemophilus was necessary in order to achieve relief of symptoms. All observers are agreed, however, that though the bacteria have been reduced to vanishing-point, the patient with chronic bronchitis will again develop bacteria in the sputum as soon as he returns home. Often also the sputum increases in amount. The importance of family infections such as colds and pharyngitis in promoting recolonization of the lower respiratory tract cannot be overstated.

Conclusion

Rous (1943) and Rous and Friedewald (1944), when discussing the relative roles of neoplastic viruses and of chemical carcinogens, drew a distinction between an actuating cause, which persists throughout the course of a disease process, and one which exerts a provocative action, leading to or promoting the development of lesions, but which subsequently disappears from these lesions. It is clear that no one has yet found an infective agent which could with confidence be described as an actuating cause of chronic bronchitis. But no one who watches the course of a group of cases of this malady can doubt the manner in which acute respiratory infections, from the simplest cold to the full-blown case of pneumonia, promote destruction of the defence of the respiratory tract and add further damage to that already present in the bronchitic subject. The subsequent chronic colonization of the lower respiratory tract, due perhaps to an inability to rid the bronchi of normally inhaled organisms, furnishes a constant source of irritation to the epithelium, and frequently causes an active inflammatory reaction. The viewpoint thus reached is that in chronic bronchitis there is essentially a failure of defence of the lower respiratory tract against invasion by nasopharyngeal organisms. The repetitive attacks of respiratory viruses to which we are all subject may play a large part in bringing about this state of affairs.

Acknowledgement

The terramycin used in this work was a gift from Messrs. Pfizer, Inc., New York, and was kindly supplied by Dr. Gladys Hobby.

Summary

1. Bacteriological observations were made upon 113 patients (90 men and 23 women) who had chronic bronchitis with or without heart failure and were admitted to hospital in Sheffield between 1949 and 1952.
2. The pneumococcus was a frequent inhabitant of the sputum in all phases of the disease. Other species of a potentially pathogenic character were less frequent, but selective media favouring *Haemophilus influenzae* were not employed.
3. Influenza-virus infection was detected chiefly in relation to the acute exacerbations of chronic bronchitis, but infection was not invariably accompanied by clinical relapse.
4. The types of pneumococci found in the sputum were spread throughout the range of the species, and the distribution resembled that found in the nasopharynx of normal individuals more closely than that found in the sputum in cases of pneumonia.
5. Treatment with antibiotics exerts a definite effect on the quality and quantity of the sputum in chronic bronchitis.
6. The evidence in favour of the view that the organisms found in the sputum in chronic bronchitis are concerned in producing an infective process is briefly discussed.

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INNATE FUNCTIONAL DEFECTS OF THE RENAL TUBULES, WITH PARTICULAR REFERENCE TO THE FANCONI SYNDROME¹

Cases with Retinitis Pigmentosa

By W. P. U. JACKSON AND G. C. LINDER

(From the Departments of Medicine and Chemical Pathology,
University of Cape Town)

With Plates 12 and 13

THE function of the renal tubules is threefold: first, reabsorption, particularly of water, glucose, chloride, phosphate, and bicarbonate, sodium, potassium, and calcium, aminoacids, and probably albumin; secondly, secretion of exogenous creatinine and certain other substances such as potassium in ordinary circumstances, and of diodrast and dyes such as phenol red under experimental conditions; thirdly, the formation of ammonia, and exchange of hydrogen for sodium ions, which reduce the loss of fixed base in acid elimination. Fanconi (1931, 1936) was the first to suggest that derangement of some of these functions could account for certain obscure syndromes with rickets. The syndrome named after him comprises essentially vitamin-D resistant rickets with low serum-phosphate, normal serum-chloride, glycosuria, and aminoaciduria. Frequently there are albuminuria, chronic acidosis, and neutral or alkaline urine with a high ammonia content. The disability is severe, and ends in glomerular failure or hepatic cirrhosis and death. Cystine deposition in internal organs is frequent. A diminished tubular reabsorption of phosphate is believed to account for the hypophosphataemia and rickets. The second osteonephropathic syndrome ascribed to specific tubular deficiency is hypophosphataemic, hyperchloraemic rickets, with much-reduced ammonia formation, chronic acidosis, and nephrocalcinosis (Butler, Wilson, and Farber, 1936). McCune, Mason, and Clarke (1943) pointed out that Fanconi's concept of specific tubular defects of function may be of importance in other syndromes, apart from those including rickets. We attempt in the present paper to consider this hypothesis, and to discuss the interrelationship of the various defects of tubular function, with particular reference to certain cases investigated in Cape Town.

Cases 1 and 2 (Plate 12, Fig. 2)

Jan was first seen at the age of 10 years. He had been deaf and dumb since birth. His development otherwise did not seem abnormal to his parents until nine months before his admission, when he was observed to be knock-kneed and more tired and less energetic than before. His movements and gait became

¹ Received July 8, 1952

stiff and restrained. On examination he was undersized (Plate 12, Fig. 3), 44½ in. tall (normal for his age is 51 in.), and weighed 47 lb. (normal 63 lb.). The penis was tiny, and no testicles were felt. There was enlargement at the ends of the long bones, without any evident skull abnormality or rachitic 'rosary'. X-rays demonstrated active rickets at the ends of the long bones (Plate 13, Fig. 4), while the skull and ribs appeared normal. Ophthalmoscopic examination revealed gross bilateral retinal degeneration, with atrophy of the disks, and such extreme attenuation of the retinal vessels that they disappeared entirely a short distance from their respective disks. The choroidal vessels were clearly visible, and appeared unaffected. The whole retinal surface was diffusely, thickly, and uniformly covered with small rounded granules of a pale brown pigment. This appearance corresponded clinically with peripheral constriction of his fields of vision, while central vision was at least good enough for him to take a pin by the point when held before him. The presence of active rickets at the age of 10 years in an undersized patient, who had good food and plenty of sunshine, naturally led to an investigation of the cause and an examination of the rest of the family. It was disclosed that Jan's parents were second cousins, and that he had a sister Anna, also deaf-mute from birth. Both parents and two other sisters were normal in history, by X-ray, and by urine examination for sugar, albumin, and calcium.

Anna was of normal height and weight for her age of four years, and showed no clinical or radiographic evidence of rickets. She showed exactly the same type of retinal degeneration as Jan, but it was less advanced, and her vision did not appear to be affected at all. In other ways the resemblance of Jan and Anna was remarkable (Plate 12, Fig. 2). Both had very blue eyes, fair hair, and freckles. Both had brachycephaly and a fat, round face, with a broad, flat nose, and good teeth. Their skin was very dry, and the subcutaneous tissue was excessively thick and podgy, so that iliac-crest marrow biopsy could only be done with the guard removed and the needle thrust as deeply as possible. Both had small, incurved little fingers (clinodactyly). Both were attending a school for the deaf, and both were considered to be backward, even allowing for their disability; Jan was considerably more backward than his sister. They were alike also in disposition, being cheerful, happy, smiling, and confiding—the 'ward pets'. On the other hand, Jan and Anna did not noticeably resemble the other members of the family. Apart from their similarities, Jan did not look a healthy child; his complexion was pasty, his skin flaky, and his muscles hypotonic and not very powerful.

Special features of serum chemistry (Table I). The changes found in Jan's serum were characteristic of active rickets: low serum inorganic phosphorus, variable (low or normal) calcium, and raised phosphatase. The only abnormal finding in Anna was a serum-phosphatase of 45 units on one occasion and of 18 on another; it was normal on four occasions. The phosphorus was normal on several examinations made months apart. Except for the two phosphatase readings, she showed no evidence of rickets either in the blood or in bone X-rays. Serum-chloride in both children was normal. Jan's alkali reserve was consistently slightly below normal, and the serum pH was just to the acid side, indicating a mild continuous state of acidosis. There were no crises of acidosis, such as occur in the full-blown Fanconi syndrome. The sum of the cations determined in the same specimen of serum was 150 mEq. (Na 141, K 3·9, Ca 5·1) and of the anions 142 mEq. (Cl 102·7, HCO₃ 23·3, P. 2·5, protein 13·5). The 8 mEq. of base unaccounted for represents the base bound by organic acids and sulphates. There was thus no definite increase in serum organic acids. The sodium, potassium, calcium, and magnesium all tended to

be at the lower limit of, or just below, the normal range. This may be correlated with the mild acidosis. The potassium was always at the lowest limit of normal. The serum-cholesterol was raised in both children; though not to the levels

TABLE I
Cases 1 and 2: Serum Investigations

	<i>Jan</i>	<i>Anna</i>
Calcium (mg./100 ml.)	6.8-10.2-*13.4	9.3-12.2
Inorganic phosphorus (mg./100 ml.)	2.2-3.5-*4.3	4.1-5.2
Phosphatase (Bodansky-Shinowara units)	22-88	8-45
Chloride (mEq./l.)	97-106	97
Bicarbonate (mEq./l.)	20-21	23
pH	7.38-7.40	..
Aminoacids	Normal	Normal
Sodium (mEq./l.)	135-143	..
Potassium (mEq./l.)	3.3-3.6	3.7
Magnesium (mg./100 ml.)	1.8	..
Cholesterol (mg./100 ml.)	277-344	201-349
Creatinine (mg./100 ml.)	1.55 (1950) 1.65 (1951)	..
Creatine (mg./100 ml.)	1.04 (1950) 1.22 (1951)	..
Urea (mg./100 ml.)	29-37	19-28
Albumin (gm./100 ml.)	4.9	4.1
Globulin (gm./100 ml.)	2.1	2.9

* Hypervitaminosis D.

found in nephrosis. This feature has not previously been reported in congenital tubular defects.

Special features of urine chemistry (Table II). *Glycosuria*, present in Jan only, was slight and variable, and bore no relation to the level of the blood-sugar.

TABLE II
Cases 1 and 2: Urine Chemistry

	<i>Jan</i>	<i>Anna</i>
Glycosuria (gm./day)	1-3	None
Albuminuria (mg./day)	100-500	100-2,000
Specific gravity: maximum	1,010	1,014
" " minimum	1,001	1,000
Colour (restricted fluids)	Pale	Rather pale
Volume (l./day)	1-1.5	About 1
Day/night volume	Equal	..
Water diuresis	Reduced	Normal
pH	5.6-6.5	5.6-6.5
Phosphorus (mg./day)	400	350
Calcium (mg./day)	10	10
Magnesium (mg./day)	70	32
Ammonia (mEq./day)	13-38	18-40
Aminoacid nitrogen	3% of total N	Slight increase
Bicarbonate	Normal	Normal
Organic acid (mEq./day)	34-48	35-45
" " (mEq./kg./day)	1.6-2.2	1.8-2.3

Diabetes mellitus has occasionally been reported in tubular rickets (Stowers and Dent, 1947), but Jan's fasting blood-sugar was only 76 mg. per 100 ml., rising to 130 mg. after 50 gm. glucose, and falling to 105 mg. in two hours. The sugar was fermented by yeast, and gave a chromatographic spot identical with that of glucose. Bial's test for pentose was negative.

Albuminuria in both children was uninfluenced by lordotic or kyphotic posture, resting in bed, sleep, activity, or time of day (compare Bull, 1948-9). With the passage of time Anna's albuminuria has increased considerably.

Concentration was low in both children, yet their daily urine volumes were not increased. Jan was noticed to pass as much urine in the night as in the day. Dilution was normal (specific gravity, 1,001), but Jan's water diuresis was somewhat defective; he passed one-half of an ingested pint of water in the next four hours, a response much below that of three control children tested at the same time.

Renal function (Table III). The clearances are given as found, and also as a mean figure corrected to a standard body-surface of 1.73 sq. m. The creatinine

TABLE III
Cases 1 and 2: Renal Function

	Jan	Anna	Normal
Creatinine clearance (ml./min.):			
20-minute periods	31, 28
mean corrected	56	..	120
24-hour periods	22-26	27-32	..
mean corrected	46	72	120
Thiosulphate clearance (ml./min.) .	18.7, 18.4
mean corrected	35	..	120
p-aminohippurate clearance (ml./min.)	79, 47
first reading, corrected	151	..	500
Phenolsulphonephthalein excretion after 6 mg. intravenous (mg./15 min.)	0-0.2	0-0.2	1.5
Response to acid : : : :	Defective	Normal rise in (see text)	..
		acidity and ammonia	

Notes.—The 24-hour clearances are, as usual, lower than the short-period ones.

'Mean corrected' is the mean corrected to a body-surface of 1.73 sq. m.

The second figure (47) obtained for C_{PAH} is almost certainly low because of the elevation of the serum level above that at which PAH could be entirely cleared by the kidney; it is therefore discounted.

and thiosulphate clearances indicate that Jan had a very poor glomerular filtration rate. The PAH clearance shows a low effective renal plasma-flow. Calculation of the ratio C_{thio}/C_{PAH} indicates a normal filtration fraction. Jan's glomerular function was thus severely depressed in addition to his tubular defect. Anna also showed evidence of glomerular damage, and her tubules were very defective as indicated by the sulphonephthalein excretion.

Reaction and ammonia. Although both children could produce urine with a pH under 5.6, their usual specimens had a reaction approaching 6.5. In spite of this the excretion of ammonia was usually 15 to 20 mEq. per day, and sometimes considerably more. Peters and Van Slyke (1931) give 35 to 70 mEq. per day as the normal ammonia excretion of an adult, which would be equivalent to 12 to 25 mEq. per day in children such as Jan and Anna on a 1.73 sq. m. basis. Their estimated excretion of ammonia in a urine of low acidity was not due to ammoniacal fermentation, since there was no evidence of urinary infection, and analyses of specimens were made immediately.

Aminoacids. Both children's urine contained about 210 mg. a day of amino-acid nitrogen by Malfatti-Sorensen titration; this is not of itself abnormal. The total nitrogen excretion was 6 gm. per day, and the index proposed by Dent (1947), $\frac{100 \times \text{aminoacid N}}{\text{total N} - \text{aminoacid N}}$, was 3.6; it should be under 3. There was

therefore a suggestion of heightened aminoacid excretion. Single-run chromatograms did not show a definite increase. Dr. Bickel of Birmingham kindly investigated samples of urine and tungstic-acid filtrates of plasma, and his conclusion was: 'I think there is a moderate but definite aminoaciduria in these two children. The pattern of the chromatogram looks to me different from

TABLE IV
Case 1: Tubular Reabsorption of Phosphate

	Tubular reabsorption			Excretion		Phosphate clearance (ml./min.)	
	Filtration rate (mg./min.)	(mg./min.)	(%)	(mg./ml. of filtrate)	(mg./min.)		
Jan (Case 1)	{ 0.414	0.128	31	0.0088	0.286	69	13.0
	{ 0.405	0.167	41	0.0091	0.238	59	10.8
Normal	96	(lowest found)	..	3.5	4.6
(Lambert, van Kessel, and Leplat, 1947)							(Cooke, Barclay, Govan, and Nagley, 1947)

Jan's serum inorganic phosphorus at this time was 2.2 mg./100 ml.

that in the Fanconi syndrome, where the increase of aminoacid excretion concerns all the aminoacids more evenly.' Dr. Bickel's full report is given in the Appendix.

Organic acids. Van Slyke and Palmer (1920) found the normal excretion of organic acids in young men to be between 0.47 and 0.96 mEq. per kg. body-weight per day. Jan's excretion was estimated from the difference of cations and anions in his urine (Table VII, line 12) and was found to be from 1.6 to 2.3 mEq. per kg. By Van Slyke-Palmer titration both his and Anna's excretion

TABLE V
Cases 1 and 2: Metabolic and Miscellaneous Investigations

	Jan	Anna
Calcium balance (intake 800 mg./day)	+ 56 mg./day	..
Phosphorus balance (intake 950 mg./day)	+ 200 mg./day	..
Fat absorption (intake 60 gm./day)	94.4%	Normal
Chloride absorption	Normal	..
Basal metabolic rate (corrected to 1.73 sq. m. body-surface).	- 28%	- 41%
Blood count	Normal	Normal
Gastric secretion	Free HCl present	..
Bone-marrow	No cystine crystals	..
Eyes	No cystine crystals	..
Urinary tract	Intravenous pyelo- gram and cysto- scopy normal	Normal

was somewhat higher. There was therefore a small but definite increase in organic-acid excretion.

Calcium. Both Jan and Anna excreted a minute amount of calcium in the urine, less than 10 mg. per day. This was an unexpected finding.

Phosphorus. The urinary phosphorus output was not high. Jan excreted a nearly constant amount of 300 to 400 mg. per day, although his serum inorganic phosphorus varied from 2.2 to 3.5 mg. per 100 ml. His phosphate excretion was studied in detail at the same time as the thiosulphate clearances (Table IV). Consecutive 20-minute collections of urine were made by catheter. At that time the serum-phosphorus was 2.2 mg. per 100 ml. The filtration of phosphorus was at the mean rate of 0.41 mg. per minute, the mean reabsorption

0.15 mg. per minute, and the mean excretion 0.26 mg. per minute; thus 36 per cent. of the phosphate filtered was reabsorbed, and 64 per cent. was excreted. The mean phosphate clearance was 12 ml. per minute. Anna's renal function and excretion of phosphate were not studied in such detail. From her serum level of 5.2 mg. per 100 ml. and her 24-hour phosphate excretion it appears that her phosphate clearance was about 4.7 ml. per minute, which is within normal limits (Cooke, Barclay, Govan, and Nagley, 1947).

Other metabolic investigations (Table V). Jan's calcium and phosphorus balances have been checked by comparison with the standard balances, in relation to intake, obtained from Mitchell's (1939) formulae. The predicted calcium excretion was 28.9 mg. per kg. body-weight, and that actually found was 36.3 mg.; Jan therefore excreted one-third more calcium than he should, and in view of his small urinary excretion the fault must have lain in a low net intestinal calcium absorption. As regards phosphorus the situation was better; on his intake he should have excreted 33 mg. per kg., and he actually excreted 35 mg. per kg. body-weight. Fat absorption was good, and steatorrhoea is excluded as the source of Jan's troubles. The low basal metabolic rate of both children was deduced from good graphs, and was checked by repetition.

Case summaries and diagnosis. Rickets at the age of 10 years, with glycosuria, led us to suspect that Jan might be suffering from the Fanconi syndrome. This syndrome appears to be almost invariably accompanied by aminoaciduria, and usually by internal deposition of cystine (Bickel, 1950). In spite of careful search we have been unable to detect any cystine deposit. Jan therefore has hypophosphataemic rickets, and evidence of incomplete renal tubular reabsorption is given by the glycosuria and high phosphate clearance, which most authors (Dent, 1950; Albright and Reifenstein, 1948; McCune, Mason, and Clarke, 1943) believe to be the fundamental defect causing rickets in the Fanconi syndrome. There is a mild aminoaciduria and excess of unidentified organic acids, also probably due to diminished reabsorption. There is a very low urinary excretion of calcium, an almost total inability to excrete phenol-sulphonephthalein, an inability to concentrate urine, and a normal resting production of ammonia with a defective reserve in response to ingestion of acid (see page 145). The tendency to a low level of fixed base in the serum and mild acidosis might be explained by incomplete reabsorption of cations. These biochemical abnormalities can all be explained by defective renal tubular function, but in addition considerable glomerular damage is indicated by the low creatinine and thiosulphate clearances. His constant albuminuria is further evidence of renal damage. Jan's condition falls under the descriptive general heading of hypophosphataemic glycosuric rickets, but his sister Anna is very different, having neither low serum-phosphorus, glycosuria, nor rickets. Yet she certainly has the same basic condition as Jan in a milder form. As evidence of defective tubular function she has poor urinary concentration, very poor excretion of sulphonephthalein, and the same type of aminoaciduria. Her hypocalciuria is of the same order. Her glomerular function as judged by 24-hour creatinine clearances is also defective, and her albuminuria is increasing as time passes. The high serum-cholesterol and low basal metabolic rate of both children have less evident relation to tubular defects, although the same triad is found in

nephrosis. Their deaf-mutism, retinal degeneration, clinodactyly, and physical similarity appear to have no connexion with renal disease. Bickel (1950) remarks on the mutual resemblance of sufferers from the Fanconi syndrome, and his description of the common features fits our patients: 'They are all remarkably colourless with scanty fair hair, a pale puffy skin, and hypotonic muscles.' The question whether the condition shown by these children is con-

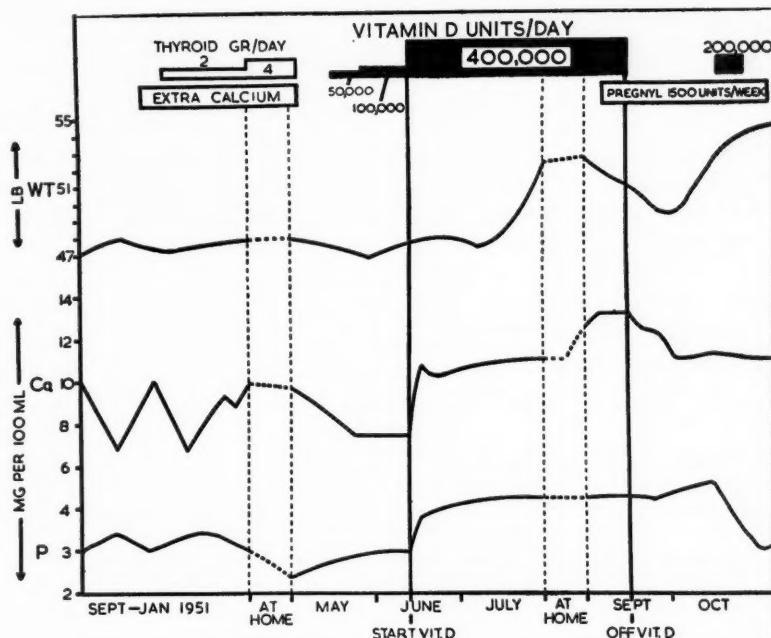


FIG. 1. Progress of Jan (Case 1) as shown by body-weight, serum-calcium, and serum-phosphorus.

sidered a form of the Fanconi syndrome is beside the point. Their condition plainly belongs to the general group of multiple defects of tubular function. In their case the defects are associated with defective glomerular function, a feature which is probably common in the Fanconi syndrome. A diagnosis of hypothyroidism was considered in both children because of the high serum-cholesterol, low basal metabolic rate, mental backwardness, and thick subcutaneous tissue. Their history, behaviour, pulse-rate, and glucose tolerance, Anna's normal height and bone development, and their lack of response to thyroid treatment, did not substantiate this diagnosis. Jan's sexual infantilism could be explained by his chronic ill health, while his stunting and delayed bone-development were directly due to his rickets. Hypopituitarism was also considered, but this diagnosis could not be upheld.

Response to therapy (Case 1). The course of Jan's condition, as mirrored by his body-weight, serum-calcium, and serum-phosphorus, is shown in Fig. 1.

During the eight months before calciferol therapy they showed little change, though there were fluctuations from week to week in the calcium reading. The serum-phosphorus remained fairly constant at a moderately low level. Serial X-rays of the wrist revealed no change in the rachitic picture, and the apparent bone age, judged by the number of epiphyses, remained at three to four years (Caffey, 1945). During this period, with a high-calcium (2 gm. per day) and a high-protein diet, there was a retention of 500 mg. of calcium and 560 mg. of phosphorus a day, and the calcium excretion agreed more closely with Mitchell's (1939) prediction. Yet this régime produced no clinical or

TABLE VI

Case 1: Effect of Vitamin D on Calcium and Phosphorus Metabolism

	Urine phosphorus (mg./day)	Serum inorganic phosphorus (mg./100 ml.)	24-hour phosphorus clearance (ml./min.)	Urine calcium (mg./day)	Serum calcium (mg./100 ml.)
Before vitamin D	320	2.5	9	10	10.2
After vitamin D (400,000 u./day):					
Days 1-3	370
" 4-6	470	3.9	9.5	19	11.3
" 7-10	470	21	..
" 11-14	610	4.2	11.4	40	10.5
" 15-18	440	4.3	8	60	10.6
11 weeks	500	4.3	9	200	13.4

biochemical evidence of improvement in two months. Thyroid up to gr. 4 per day likewise caused no discernible change. Vitamin D (calciferol) was then used, but no response to 50,000 or to 100,000 units a day was seen after 10 days of each dose. With 400,000 units a rise of serum-phosphorus occurred within five days, the serum-calcium was stabilized, after four weeks the weight began to rise, and within another two weeks Jan had gained 5 lb. After 10 weeks of this dose an X-ray of the wrists (Plate 13, Fig. 5) showed the rickets to have healed, and three new carpal centres had appeared. In general Jan was much improved, more lively, moving more easily, playing more readily, and acting more normally. His parents were delighted with the change in him. Other effects of these large doses of vitamin D included a rise of the blood pH and CO₂-combining power to normal levels, and a rise of fixed base. The calcium output in the urine began to increase, and after 11 weeks the serum-calcium rose to over 13 mg. per 100 ml. and Jan began to lose weight. These danger signals were heeded, and the vitamin was stopped. The chart (Fig. 1) shows a rapid decline of serum-phosphorus, and it seems likely that calciferol therapy will have to be resumed. Vitamin D had no effect on the serum-cholesterol. The albuminuria and glycosuria were unaltered. The level of serum-phosphatase remained high.

Vitamin D and phosphate retention. The large doses produced a very rapid rise in serum-phosphorus. Daily urine analyses showed no decrease, but an immediate rise, in urinary phosphorus (Table VI). Since the level of serum-phosphorus rose at the same time, and bony calcification followed, an increased net phosphate absorption from the gut must have been a primary manifestation. There was no change in renal phosphate clearance.

Vitamin D and urine calcium. The Table shows that the urinary calcium excretion rose from 10 mg. to about 200 mg. per day. As in the case of phosphorus, there must have been improved intestinal absorption.

Discussion (Cases 1 and 2)

Glomerular damage is generally supposed to occur only late in the Fanconi syndrome, as a sequel to cystine deposition or, in some ill-defined way, to continued passage of excessive amounts of organic acids or other substances. Autopsies have several times shown considerable glomerular defect, even when death has not been due to uraemia (McCune, Mason, and Clarke, 1943). Accurate methods of assessment have seldom been applied during life, for it has been incorrectly assumed that a normal blood-urea and a normal response to simple 'function' tests exclude glomerular damage. Apart from our patients (Table III), we have found exact modern tests of function applied only to the patient of Milne, Stanbury, and Thomson (1952), in whom glomerular function was seriously impaired. Stowers and Dent (1947) found the standard urea clearance in their adult patient to be 26 per cent. of mean normal, but they investigated it no further, and merely commented that it might have been affected by alkali therapy. It seems not unlikely that many patients with the Fanconi syndrome have primary defects in the glomeruli as well as in the tubules, although the effects of the latter are more outstanding. Jan may be such a patient, and Anna may have the same condition in a less developed form. This conception suggests that the Fanconi syndrome and the better-known 'renal rickets', with more prominent glomerular failure, are less definitely separated than is usually believed. It also brings to mind the various aspects of 'familial nephritis', well documented by Osman (1927), Hurst (1923), and Hawkins and Smith (1950). The family described by Hawkins and Smith showed other hereditary abnormalities.

Phosphorus: diminished tubular reabsorption and effect of vitamin D. It is agreed that, at normal and low levels, all the serum inorganic phosphorus is ultrafiltrable (Smith, 1951); this justifies the analysis of phosphate excretion on clearance lines. Harrison and Harrison (1941) and Pitts and Alexander (1944) have shown that in dogs the tubules have a limited reabsorptive capacity for phosphate, (T_m), which is reached when the serum and glomerular filtrate contain between 3.3 and 4.6 mg. of phosphorus per 100 ml.; above this level the excess filtered is quantitatively excreted. There is no sharp threshold for phosphate, but a zone between 3 and 2 mg. phosphorus per 100 ml. of serum through which the phosphorus excreted falls slowly to its lowest level. At this level the urine of dogs contains less than 1 per cent. of the phosphorus which is filtered through the glomeruli, and Lambert, van Kessel, and Leplat (1947) found that normal young women in this threshold zone excrete 3 to 5 per cent. of the phosphorus filtered. Hence Jan's excretion of 60 per cent. of his filtered phosphorus (Table IV) at a serum level of 2.2 mg. per 100 ml. was extremely high, and his tubular reabsorption of 0.009 mg. of phosphorus per ml. of glomerular filtrate was much lower than that found by Lambert and his colleagues in normal subjects, among whom the lowest reabsorption was 0.021 mg. per ml. of filtrate with a serum level of 2.4 mg. per 100 ml. In other words Jan's urinary output of phosphate was high in relation to its serum level, and

this increase was caused by poor tubular phosphate reabsorption. Jan's rickets may have been due at least partly to hyperphosphaturia, which may have been larger in the earlier stages of his disorder, when the serum-phosphorus and the load of filtered phosphorus on his tubules were probably greater. Hyperphosphaturia is generally stated to be the cause of the rickets in vitamin-D resistant rickets and the Fanconi syndrome, but has seldom been adequately demonstrated. Anna's phosphorus clearance was about 4.7 ml. per minute, which is within the normal range (Cooke, Barclay, Govan, and Nagley, 1947), and corresponds with the absence of rickets in her case. Extrarenal influences must also be considered. Jan's rickets may have stimulated his parathyroids to attempt to maintain normal levels of calcium in the serum at the expense of increased phosphate excretion (Albright, Bauer, Ropes, and Aub, 1929). Most recent work has failed to show that parathyroid hormone influences tubular reabsorption; it follows that the increased excretion would have to be attributed to increased filtration (Smith, 1951), but such an explanation could hardly apply to a child with Jan's known glomerular limitations.

Harrison and Harrison (1941) showed that vitamin D has an immediate effect in increasing phosphate reabsorption; Jan's lack of renal response to this vitamin has been described (Table VI), and his increased absorption of phosphorus from the gut agrees with the contention of Albright, Burnett, Parson, Reifenstein, and Roos (1946), and Albright and Reifenstein (1948) that the main action of vitamin D is to raise the alimentary absorption of calcium and phosphorus. Freeman and Dunsky (1950) reached the same conclusion in their case of resistant rickets. On the other hand, Kadji (1944) and McCance (1947) found a raised renal threshold for phosphorus in cases of resistant rickets on massive calciferol therapy, with consequent lowering of urinary phosphate excretion. Dent (1950) also thought that vitamin D increases the reabsorption of phosphate in the Fanconi syndrome. Robinson and Nelson (1945) found a diminished urinary phosphorus after treatment, but ascribed it to decreased glomerular filtration. In the case of vitamin-resistant rickets (? incomplete Fanconi syndrome) described by James and Dunn (1951) there was bony healing on treatment with calciferol, without any rise in serum-phosphorus, while Anderson, Miller, and Kenny (1952) found that the phosphorus balance of an adult patient with the Fanconi syndrome was not improved by increasing the dose of vitamin from 12,000 to 250,000 units a day.

Calcium: hypocalcuria. Jan and Anna excreted a minute amount of calcium in their urine, less than 10 mg. per day, and in this they differed from other members of their family (sisters, mother, father) who excreted over 100 mg. per day. The cause is obscure, since owing to the complexity of the state of calcium in the serum this substance cannot yet be submitted to rigorous excretion-analysis by the clearance technique (Smith, 1951). The possibilities must, however, be a very low glomerular filtration, a very high tubular reabsorption, or a combination of both factors. Such low urinary excretion of calcium has been reported by Bickel (1950) in a case of the Fanconi syndrome. Pedersen and McCarroll (1951) found a similar condition by the Sulkowitch

test in vitamin-resistant rickets with a normal serum-calcium. It may also occur in the nephrotic syndrome (Emerson and Beckman, 1945) and in pseudo-hypoparathyroidism (Elrick, Albright, Bartter, Forbes, and Reeves, 1950). Nephrosis is certainly, and pseudohypoparathyroidism may be, associated with severe defects of tubular function (see page 150). It seems likely that the low urinary calcium is due to excessive tubular reabsorption, and there is no reason to suppose that a reduced reabsorption of some substances may not be accompanied by an increased reabsorption of others. The increase of urinary calcium to a more normal level with vitamin D (Table VI) must have been due either to an increase in the filtrable fraction of the serum-calcium, or to a lessening of a previously excessive tubular reabsorption.

Conclusion (Cases 1 and 2). Jan and Anna, with a very slight aminoaciduria, acid urine, and no real acidosis, are comparable to the adult patient of Anderson, Miller, and Kenny (1952), and forge another link between the classical Fanconi syndrome and the adult glycosuric hypophosphataemic osteomalacia of Milkman (1934), Hunter (1935), and Cooke, Barclay, Govan, and Nagley (1947). All such cases are examples of multiple innate defects of tubular function.

Cases 3 and 4 (Reported in full by Linder, Bull, and Grayce (1949))

Case 3. H. M. was a coloured girl, aged 13 years at the time of investigation. For about five years her vision had progressively deteriorated, and there had been painless swelling of joints and bony deformity. She was below the normal height and weight, and showed clinical and radiological stigmata of active rickets, with porosis and numerous greenstick fractures. In the eyes the fundi showed changes characteristic of retinitis pigmentosa. No cystine crystals were seen. Sugar, which was proved to be glucose, was almost always found in the urine. The glucose-tolerance curve was normal. There was no albuminuria. There was a persistent polyuria of two to five litres a day. The specific gravity of the urine ranged from 1,002 to 1,008. Posterior pituitary extract had no effect on the water excretion. The blood-urea remained low. Urea clearance was within the normal range, but there was gross deficiency of phenolsulphonephthalein excretion, indicating defective tubular function. The serum-calcium varied from the low figure of 7.6 mg. to 10.9 mg. per 100 ml. Two early examinations of the serum-phosphorus gave high readings, 7.2 mg. and 5.9 mg. per 100 ml., but later readings fell to about 2 mg. per 100 ml. The serum alkaline phosphatase level was always high. The serum-chloride was normal, and there was no difficulty in excreting excess chloride in the urine. The serum-bicarbonate was just below normal, and the pH normal. The urine was always acid, with normal ammonia and bicarbonate content, but with two or three times the normal amount of organic acids. Aminoacid excretion was greatly increased. The urinary aminoacid nitrogen was 20 per cent. of the total nitrogen; Dent (1947) gave the normal figure as 1.2 per cent. Dr. C. E. Dent examined a sample of urine by two-way chromatography, confirmed the great excess of aminoacids, and showed that many different acids were involved. Only a slight increase in cystine was found. The serum aminoacid nitrogen was low (2.95 mg. per 100 ml.). Calciferol, 500,000 units a day, raised the serum-phosphorus from about 2 mg. to 3.7 mg. per 100 ml., but little clinical and no radiological improvement was seen after several months. H. M. has since died

at home; details of her latter days are not available, and no autopsy was performed.

Family history. H. M. had eight brothers and sisters. The parents were not related, and there was no history of poor sight or bony abnormality in any of the siblings, parents, uncles and aunts, or nieces and nephews, except in the case of one sister, D. M. (Case 4).

Case 4. There can be little doubt that D. M. also suffered from both retinitis pigmentosa and the Fanconi syndrome. She was in hospital in 1933, at the age of 16 years, with pathological fractures of the femurs. She had teethered, walked, and talked at the usual ages, and had been well until 1933, when her sight became weak, and her legs lost their strength to such an extent that she had to use crutches. In December 1936 both femurs were fractured, and a radiologist reported that the bones showed pronounced osteoporosis, with a very thin cortex and the bony trabeculae practically invisible. In March 1938 she was thin and under-developed. All the bones showed decalcification and osteoporosis, with recent fractures of the femurs. Her eyes showed bilateral optic atrophy and retinitis pigmentosa. Albuminuria and glycosuria were present, but were not adequately investigated. There was no ketonuria. Her serum-calcium was 9.7 mg. per 100 ml., serum inorganic phosphorus 2.1 mg. per 100 ml., and phosphatase 13.7 Kay units. The Wassermann reaction was negative. It was assumed that she had diabetes, and a diet was given with 20 units of insulin a day. She was transferred in plaster to a home for cripples. In August and October 1938 the blood-sugar was observed to be 171 and 136 mg. per 100 ml., and her serum-calcium was 11.2 mg. per 100 ml. She died in 1939, and her death was attributed to diabetes.

Diagnosis of Cases 3 and 4. H. M. plainly suffered from the Fanconi syndrome, with late vitamin-D resistant rickets, hypophosphataemia, glycosuria, and aminoaciduria. In addition her polyuria was evidently nephrogenic in type, and may be explained by deficient water reabsorption in the distal convoluted tubule or in the loop of Henle, or both. A high, rather than low, serum inorganic phosphorus is occasionally reported at certain stages of the Fanconi syndrome (Hottinger, 1941; Danis and Rosen, 1941), and cannot be explained by glomerular renal failure with phosphate retention, since the non-protein nitrogen is quite normal. Unlike the state of affairs in the typical Fanconi syndrome, H. M. was not acidotic, and suffered from no febrile crises. Her production of ammonia was poor, whereas in the Fanconi syndrome it is usually increased.

Acid-Base Regulation (Case 1, Jan, and Case 3, H. M.)

Reaction, ammonia, bicarbonate, and titratable acidity of urine. In the classical Fanconi syndrome the urine never becomes acid, although it contains much ammonia. Unusual fixity of reaction is also a feature of hyperchloraemic renal rickets with nephrocalcinosis, but in this condition ammonia formation is defective (Baines, Barclay, and Cooke, 1945). According to Latner and Burnard (1950) the essential feature is a failure of the proximal tubules to reabsorb bicarbonate from the glomerular filtrate. The presence of so much bicarbonate in the distal tubule inhibits the formation of ammonia, and when the normal exchange of hydrogen for basic ions in the tubule takes place a large amount

of carbonic acid is formed; this is the consequence of the increased proportion of bicarbonate to phosphate in the tubular lumen. The final result is a very high pressure of carbon dioxide in the urine excreted. Although Jan's serum-chloride was usually normal, it occasionally reached a high level (106 mEq. per litre), so that an investigation of his bicarbonate excretion seemed pertinent. For a number of days in October 1951 the reaction of every specimen of urine was tested immediately, either electrometrically or by means of 'accutint' test papers; the samples were then covered with paraffin and refrigerated, and the CO₂ content was later determined in the Van Slyke gas apparatus. From the pH and the CO₂ content the amount and pressure of free CO₂ were calculated (Sendroy, Seelig, and Van Slyke, 1934). Jan's urine pH varied from 5.6 to 6.6, and after taking ammonium chloride he passed a specimen with a pH of 5.38 (glass electrode). The highest bicarbonate concentration was 3.7 mEq. per litre with a pH of 6.6; the lowest pH was 5.38, and the highest CO₂ pressure 60 mm. of mercury, but in only one other of the large number of tests was the pressure above 40 mm. In Jan, therefore, the mechanism described by Latner and Burnard (1950) was not operating.

Acid-Feeding Response

The first acid-feeding experiment with Jan proved unsatisfactory and contradictory; failure to absorb the acid seemed a possibility. On the second occasion a similar test was carried out with ammonium chloride as the acid load. After three control days on a constant-chloride diet with neutral ash, 2.5 gm. were given in cachets each day for six days; this dose was 2 mEq. per kg. body-weight, or 46.7 mEq. a day. In addition to the urine analyses the faeces were collected, and their chloride, sodium, and potassium content examined. Before the ammonium chloride was given there was no faecal excretion of chloride, but 2.8 mEq. of sodium and 9.8 mEq. of potassium were excreted per day. During the ammonium-chloride period the figures were respectively 2.5, 1.8, and 9.0 mEq., and during the recovery period 0.3, 0.2, and 0.5 mEq. These results show that on this occasion only 5 per cent. of the extra chloride was unabsorbed. Incidentally a great decrease in the faecal sodium and potassium was found during the recovery period. The results of the urine analyses are given in Table VII. The results of similar tests in normal persons and in Case 3, an example of the Fanconi syndrome, have been published (Linder, 1926-7; Linder, Bull, and Grayce, 1949).

Chloride. There was a prompt and progressive increase in the elimination of chloride, which may be considered as normal under these conditions, and occurred also in Case 3.

Ammonia. The urine under the control conditions contained 9.9 mEq. a day. After the ammonium chloride the quantity increased to 27.5 mEq. a day. Ammonia production seemed adequate for normal conditions, but the reserve as disclosed by the acid stress was much less than normal. In Case 3 the findings were similar. Titratable acid was normal in amount, and increased in a normal way. Base economy, the sum of ammonia and titratable acidity

TABLE VII
Case I: Urine Analyses during Acid-Feeding Experiment

	Control days			Control days (mean)			Ammonium chloride days			Recovery days	
	1			2			3			4	
	1	2	3	1	2	3	1	2	3	4	5
1. Volume (litres)	.	.	.	1.54	1.60	1.21	1.45	1.59	1.06	1.36	1.29
2. pH	.	.	.	6.0-6.6	6.0-6.5	5.8-6.5	..	6.0	6.0	6.0-5.6	6.0
3. Base bound by:											
Chloride (mEq.)	.	.	.	48.2	49.3	36.6	44.7	58.6	60.7	60.5	76.6
Sulphate (mEq.)	.	.	.	14.1	13.0	14.6	13.9	20.4	15.0	12.5	13.7
Phosphate (mEq.)	.	.	.	29.0	36.0	29.9	31.6	30.5	31.3	32.4	40.0
4. Ammonia (mEq.)	.	.	.	8.8	10.8	10.1	9.9	16.2	21.0	17.6	21.2
5. Titratable acid less bicarbonate (mEq.)	.	.	.	15.9	16.9	16.1	16.3	21.6	18.5	23.8	20.2
6. Sodium (mEq.)	.	.	.	50	47	41	43	38	42.5	39	50
7. Potassium (mEq.)	.	.	.	47	50	42	49	55	48.5	46	39
8. Calcium and magnesium (mEq.)	.	.	.	13.5	13.5	15.5	14.1	13	19	14	19
9. Fixed base (mEq.)	.	.	.	110.5	110.5	98.5	106.5	106	110.0	99	108
10. Determined acid (mEq.)											
(Cl + 2 × SO ₄ + 1.8 × PO ₄)	.	.	.	91.3	98.3	81.1	90.2	109.5	107	105.4	114.2
11. Total acid excreted (mEq.)											
(4) + (5) + (9)	.	.	.	135.2	138.2	124.7	132.7	143.8	149.5	140.4	149.4
12. Undetermined acid (mEq.)											
(11) - (10)	.	.	.	43.9	39.9	43.6	42.5	34.3	42.5	35.0	41.8
13. Base economy (mEq.) (4) + (5)	.	.	.	24.7	27.7	26.2	26.2	37.8	39.5	41.4	47.1

less bicarbonate, which in the control period was 26 mEq. per day, increased progressively in the ammonium chloride period, and reached 61 mEq. on the sixth day. This extra base economy then accounted for the elimination of two-thirds of the acid load, but on the preceding days it had accounted for only one-quarter to one-half. This is a definite but hardly a normal response, the limitation being in ammonia production.

Fixed base. There was an extra excretion of fixed base in the later days of the ammonium-chloride period, but it was no larger than may occur in normal individuals. The increase was shared equally between sodium, potassium, and the sum of calcium and magnesium, but, compared with the control excretion, the increase of the calcium and magnesium was much the largest. In Case 3 a large drain on the fixed-base resources was demonstrated.

Organic acids. In the Fanconi syndrome the presence of a large amount of organic acids in the urine has often been noted. The undetermined acid (Table VII, line 12) is an estimate of the organic-acid excretion. In Jan this estimate varied from 1.6 to 2.2 mEq. per kg. body-weight, which is twice the normal amount (Van Slyke and Palmer, 1920); it was not influenced by the ammonium chloride. Case 3 showed an excretion of similar magnitude, but it was much increased by the acid load.

Serum. After five days of the ammonium chloride the serum pH fell from 7.48 to 7.44, and the bicarbonate from 22.9 mEq. to 19.3 mEq. The chloride increased from 101 to 108.3 mEq. The serum calcium and inorganic phosphate were not changed. These small changes show good resistance to the stress of ammonium chloride acidosis.

To sum up, Jan has no excess of bicarbonate in his urine and, although his power of dealing with extra acid is limited, he manages to preserve his acid-base balance without calling unduly on his reserves of fixed base. Under ordinary conditions he can produce enough ammonia, but the reserves with which a normal person meets an acid stress seem to be very limited in him. In Case 3 ammonia production was similarly defective on acid feeding, and a large loss of fixed base was associated with greater excretion of organic acids. The investigation of both these families shows that a limitation of ammonia formation may occur in the presence of normal bicarbonate reabsorption. This limitation can therefore be a 'primary' defect of tubular function in some cases of the Fanconi syndrome, even if it may be secondary in the syndrome of hyperchloraemic nephrocalcinosis.

The Group of Innate Tubular Deficiencies

The Fanconi syndrome. Several other cases have been reported resembling the Fanconi syndrome, but differing in individual ways: without acidosis (Boyd and Stearns, 1942; Dent and Harris, 1951); without glycosuria (McCune, Mason, and Clarke, 1943; Boyd and Stearns, 1942); without rickets (Bickel, 1950; King and Lochridge, 1951); with poor ammonia production (Linder, Bull, and Grayce, 1949; Lowe, Terrey, and MacLachlan, 1952); with failure

of bicarbonate reabsorption and symptoms of hypokalaemia (Milne, Stanbury, and Thomson, 1952); with hyperchloraemia (Caussade, Verain, and Neimann, 1940); without cystinuria, though with increased output of other aminoacids (Stowers and Dent, 1947); with hyperphosphataemia but no glomerular failure (Danis and Rosen, 1941; Hottinger, 1941); with spontaneous remission (Taylor, 1951); with polyuria (Linder, Bull, and Grayce, 1949); and with fixation of urinary specific gravity (Boyd and Stearns, 1942). These various cases indicate that there is probably no single invariable finding in the Fanconi syndrome if the wider concept is used, whereas many obviously homologous cases cannot be termed 'Fanconi syndrome' if a strict definition is applied. The term 'multiple defect of tubular function' covers them all.

It is, however, impossible to explain all the features of the Fanconi syndrome on the basis of defective tubular function. In childhood it is becoming evident that the Fanconi syndrome is usually accompanied by cystine storage in the tissues at an early stage; so much so that Bickel (1950) expected to find it in every case, and considered that a pre-renal disturbance of aminoacid metabolism was the primary cause. Fanconi (1946), Dent (1947), and Rapoport (1950) have agreed that cystinosis virtually means the Fanconi syndrome, although some adult sufferers from the latter condition do not show cystine storage (Stowers and Dent, 1947), and there was no evidence of it in any of the present cases. Not all patients who have cystinosis, or an otherwise typical Fanconi syndrome, develop rickets. King and Lochridge (1951) reported that autopsy of a child, who had cystinuria and died at the age of two and a half years, disclosed systemic cystinosis and gross tubular damage without glomerular or bony changes. The causal relationship of cystinosis to defective tubular function is at present obscure. Hyperphosphaturia, which is generally assumed to be the cause of the hypophosphataemia and rickets, is seldom found, though it has been demonstrated by Gittleman and Pincus (1940) and by McCune, Mason, and Clarke (1943) that some patients, like our own Case 1, have high renal phosphate clearances. Glomerular defects may be present (see page 141), but they are not the dominant defects, and do not account for the clinical features. If they are present it cannot be certain that albuminuria, when it occurs, is not due to glomerular leakage. It is difficult to explain the occasional hyperphosphataemia, in the absence of gross glomerular failure, by any renal tubular mechanism; this led Linder, Bull, and Grayce (1949) to suggest secondary hypoparathyroidism. The very frequent inability to produce an acid urine has not been satisfactorily explained, especially in the presence of acidosis and high urinary organic-acid excretion. The serum acidosis is presumed to be due to reduction of fixed base, which is lost in neutralizing the excessive acids excreted. Finally, the appearance of hepatic necrosis or cirrhosis may be related to the continuous loss of aminoacids in the urine. Apart from these difficulties there is not only good evidence, but definite proof, of severe tubular abnormalities in the various cases which have come to autopsy (McCune, Mason, and Clarke, 1943; King and Lochridge, 1951). Stowers and Dent (1947) also found a deficiency of the enzyme phosphatase in the proximal tubules of

their patient, which might explain the poor reabsorption of phosphate and of sugar and aminoacids, the latter probably being phosphorylated before absorption.

The complicated syndrome of *hyperchloraemic nephrocalcinosis* may be capable of explanation by a single defect—lack of reabsorption of bicarbonate ions—as shown by Latner and Burnard (1950). Milne, Stanbury, and Thomson (1952) reported the Fanconi syndrome in an adult, with an increase of pCO_2 in the urine and failure to reabsorb bicarbonate. The loss of base in this case actually led to paralytic symptoms from hypokalaemia. They suggested, on the basis of chemical resemblance, an overall identity of the various tubular deficiencies. On the other hand, chemical similarities may well be produced by different underlying causes, and on the whole the various groups are clinically distinct, although they overlap in their end-results. Similarly uremia, and all its symptoms, may appear as an end-result of alkalosis, but this does not prove the latter's identity with nephritis. The great difference in inheritance of the various tubular syndromes is a strong argument against their fundamental identity. Albright and his fellow-workers (1940, 1946, 1948) suggested considerable differences in the mechanism responsible for similar chemical findings in the Fanconi syndrome and in nephrocalcinosis. They ascribed hypophosphataemia in the former syndrome to poor tubular reabsorption of phosphorus, and in the latter to hyperparathyroidism secondary to loss of calcium. The acidosis in the former condition was put down to an excess of organic acid, and in the latter to a diminished ability to excrete acids. Acidosis is not an essential feature of the Fanconi syndrome, several cases reported in the literature having shown it only in a very slight degree, as in the two families we have described; Stevenson's patient (1950), with the classical infantile Fanconi syndrome, had a CO_2 -combining power in the plasma of 54 volumes per cent. On the other hand, acidosis, with a continued drain of fixed base, appears to be an essential feature of hyperchloraemic nephrocalcinosis.

Polyuria (as found in Case 3, H. M.) has been previously reported in the Fanconi syndrome (Guild, Pierce, and Lilienthal, 1937; Hottinger, 1941; McCune, Mason, and Clarke, 1943; van Creveld, 1934). In some patients with a urine of high specific gravity it could possibly be explained by the osmotic effect of the excessive excretion of cations, acids, and glucose. The patient of Boyd and Stearns (1942) had polyuria without excessive acidity of the urine and without glycosuria, while in our Case 3, M. H., the polyuria seemed far too great to be caused by the organic-aciduria and the slight glycosuria. The patients of Danis and Rosen (1941) were unable to concentrate urine to a specific gravity above 1,008, and suffered from thirst. A primary defect of water reabsorption, producing nephrogenic diabetes insipidus insensitive to pitressin, has been reported by McCune, Mason, and Clarke (1943), and Williams and Henry (1947) found this defect in seven members of one family, in which it was inherited as a sex-linked recessive characteristic. In one case they found also a diminished serum-bicarbonate, and showed that there was grossly defective tubular excretion of diodrast and phenolsulphonephthalein. Forssman

(1945) reported the pedigrees of three families which showed diabetes insipidus with sex-linked inheritance. The disease in two families was of the usual pituitary type, but in the third it was totally insensitive to pitressin, and at least one member had renal glycosuria. Dancis, Birmingham, and Leslie (1948) isolated large amounts of antidiuretic substance from the urine of their patient, who had gross polyuria which had proved insensitive to pitressin. In our Case 2, Anna, there was no polyuria, but an inability to concentrate urine in the presence of normal glomerular function. There seems little doubt therefore that polyuria can sometimes be explained by diminished water reabsorption, with a tubular deficiency in which the end-organ (the distal renal tubule) is unresponsive to antidiuretic hormone. It is natural that this particular defect of tubular function does not necessarily stand alone, but may be accompanied by evidence of other defects, and that it is clearly related to, or may be part of, the Fanconi syndrome.

Pseudohypoparathyroidism is an interesting condition in which the biochemical changes of hypoparathyroidism (low serum-calcium and high serum-phosphate) coexist with certain skeletal abnormalities and with a lack of the normal phosphatic diuresis on giving parathormone (Albright, 1942; Sprague, Haines, and Power, 1945; Elrick, Albright, Bartter, Forbes, and Reeves, 1950). The defect is believed to be located in the end-organ which is normally acted upon by parathyroid hormone. It may thus be considered as an innate defect of renal tubular function in which there is an excessive reabsorption of phosphate.

Vitamin-D resistant rickets (Robertson, Harris, and McCune, 1942; Freeman and Dunsky, 1950) appears to be the opposite condition, in which there is an innate deficiency in reabsorption of phosphate, without the other defects associated in the Fanconi syndrome. It is remarkable that both this condition and its opposite, pseudohypoparathyroidism, can be controlled clinically and biochemically by the same treatment, namely, large doses of vitamin D (Alexander and Tucker, 1949).

It seems on the whole, then, most logical at the present time to consider the 'Fanconi group' of infantile or adult syndromes, comprising multiple innate tubular defects with and without cystinosis, to be separate from idiopathic nephrocalcinosis, and separate again from the conditions which show single tubular defects. These syndromes are all comparable in being largely explicable by specific defects of renal tubular function, but are not necessarily related as regards their primary cause. They may be listed as follows:

Unifactorial conditions:

Inability to reabsorb:

Water	Renal diabetes insipidus.
Phosphate	Vitamin-D resistant rickets, early or late (R.R.D. ² of McCance, 1947).
Glucose	Renal glycosuria.
Cystine and other aminoacids	Simple congenital cystinuria (Dent and Rose, 1951).

² Raised resistance to vitamin D.

Inability to reabsorb:

Aminoacids	Wilson's disease (hepato-lenticular degeneration).
	Galactosaemia (?) (Holzel, Komrower, and Wilson, 1952).
Calcium	Idiopathic hypercalcuria (McCune and Pray, 1940; Albright and Reifenstein, 1948).
Bicarbonate	Hyperchloraemic nephrocalcinosis.

Excessive reabsorption of:

Phosphate	Pseudohypoparathyroidism.
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Multifactorial conditions (probably all one disease, the 'Fanconi group'):

Inability to reabsorb:

Phosphate and sugar	Glycosuric rickets, or osteomalacia.
Phosphate, sugar, and amino-acids†	Fanconi syndrome.

† Often associated with:

- Inability to reabsorb water, albumin (?), and fixed base, and to form ammonia;
- Glomerular defect;
- Organ cystinosis.

Genetic Considerations

All the conditions characterized by primary deficiency of tubular function are inherited abnormalities except hyperchloraemic nephrocalcinosis, of which more than one case has not been reported in any one family. The Fanconi syndrome in infants is certainly hereditary, and probably carried by a single recessive autosomal gene. The same applies to the families of hyperphosphataemic glycosuric rickets (without glomerular failure) of Danis and Rosen (1941) and of Hottinger (1941), the latter with proved cystinosis, and to the family of Pache (1940), in which a brother and sister had non-glycosuric hypophosphataemic cystinuric rickets. In all the various groups of the 35 cases reviewed by McCune, Mason, and Clarke (1943) a familial incidence of the brother-sister type is mentioned nine times, and parental consanguinity at least five times. Adult Fanconi syndromes may be inherited differently, as in the family of Stowers and Dent (1947), where irregular dominance best fitted the data. This difference follows the general law of genetics that, where a condition can be inherited in both recessive and dominant ways, the dominant state is the milder and often shows itself later in life. 'Classical' cystinuria, without cystinosis, phosphate changes, or rickets, is always accompanied by excessive excretion of other aminoacids, and is inherited as a recessive or irregular dominant characteristic (Garrod, 1923; Thin, 1929; Dent and Harris, 1951). Wilson's disease, in which aminoaciduria appears to be a primary defect (Uzman and Denny-Brown, 1948; Dent and Rose, 1951) is probably inherited

as a recessive condition (André and van Bogaert, 1950). Simple renal glycosuria is inherited as a single dominant character (Hjarne, 1927; Bowcock, 1929; Babson, 1940). Renal diabetes insipidus seems to be inherited as a sex-linked recessive. Vitamin-D resistant rickets is clearly hereditary, and manifests itself in direct line as a dominant characteristic with good penetrance (Freeman and Dunsby, 1950; Pedersen and McCarroll, 1951). McCance (1947) distinguished infantile resistant rickets from that of later onset (R.R.D.), but the genetic features do not seem different. One of our own patients had a mild renal glycosuria as well as rickets. The few indications of inheritance in pseudo-hypoparathyroidism suggest that a dominant autosomal factor may be partly responsible, since mother and child were affected in one family (Elrick, Albright, Bartter, Forbes, and Reeves, 1950).

In our two families the renal tubular defects were associated with other inherited abnormalities. Jan and Anna, in the first family, both suffered from congenital deaf-mutism and pigmentary retinal degeneration. H. M., in the second family, suffered also from a pigmentary retinal degeneration typical of retinitis pigmentosa, and her sister D. M. was almost certainly similarly affected. No other member of either family showed any of these disabilities. Although pigmentary retinal degeneration and deaf-mutism are frequently associated in the same patient (Bell, 1922; Nettleship, 1909), or in the same family (von Wibaut, 1931; Usher, 1914), we have been unable to find any records of their combination with defects of renal tubular function. It is difficult in such circumstances to know whether these conditions in our patients are due to recessive genes linked on the same chromosome, or to a single gene with multiple effects. The same difficulty regarding the inheritance together of deaf-mutism and retinitis pigmentosa has been frequently discussed (Sorsby, 1951), but it seems likely that their combination is commonly due to a single gene. It is interesting that deaf-mutism may be combined with retinal degeneration in another syndrome mediated by a single recessive gene with multiple effects, namely, the Laurence-Moon-Biedl syndrome. Whatever the exact mode of inheritance in the families here reported, they appear to establish a connexion between innate tubular deficiencies of the Fanconi type and certain inherited diseases of the special senses, since it is unlikely that the various combinations are fortuitous. It is possible that the same gene-complex is operative in both our families, the finer points of difference in its expressivity being due to modifying factors.

There is no real evidence to link genetically the monosymptomatic tubular deficiencies with the multiple (Fanconi-like) states. The occasional occurrence of renal glycosuria, for instance, with renal diabetes insipidus and with resistant rickets is not sufficient to allow such cases to be designated *formes frustes* of the Fanconi syndrome. They may be so, but there is better evidence to the contrary, such as the genetic distinctions, the sex-linkage of renal diabetes insipidus, and the apparent non-inheritance of hyperchloraemic nephrocalcinosis. Furthermore, Brooks, Heasman, and Lovell (1949) have reported a family exhibiting both congenital cystinuria and retinitis pigmentosa, both

apparently recessive but unconnected, the carrying genes being situated on different chromosomes. This suggests that the gene concerned with congenital cystinuria is not connected with that responsible for the Fanconi-like syndrome of our second family, since the latter disease was associated with retinitis pigmentosa. Dent and Rose (1951) also concluded that the congenital cystinurias comprise a homogeneous group, without any overlap with the Fanconi syndrome or organ cystinosis, being chemically, clinically, and genetically distinct.

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APPENDIX

Methods. The methods used were those detailed in earlier papers (Linder, 1926-7; Linder, Bull, and Grayce, 1949), with the following additions:

Faecal fat	van de Kamer, Huinink, and Weyers (1949).
Magnesium	Garner (1946).
p-aminohippuric acid . . .	Smith, Finkelstein, Aliminosa, Crawford, and Graber (1945).
Sugar chromatography . . .	Horrocks and Manning (1949).
Thiosulphate	Micro-modification of Brun (1950).
Sodium and potassium . . .	Flame photometer.

Aminoacids (Cases 1 and 2). Dr. Bickel's report. 'The urine (two-way) chromatograms of both children show a slight but definite aminoaciduria. Anna shows a strongly increased excretion of glycine, glutamic acid, alanine, and lysine, much less of serine, glutamine, threonine, valine, the leucines, tyrosine, and phenylalanine. Jan shows similarly a strong glycine, glutamic acid, alanine, lysine, and glutamine excretion and less of cystine (as cysteic acid after oxidation), serine, threonine, histidine, methyl-histidine, valine, the leucines, phenylalanine, and tyrosine. Jan's chromatogram was stronger than Anna's. There was a moderate positive nitroprusside-cyanide test in the urine of both children.' Dr. Bickel then made microbiological assays of further urine samples, and found a distinct increase in threonine and phenylalanine, and possibly a slight increase in tryptophane and valine, over the normal figures. Arginine was normal.

His report on the plasma of the two children was: 'Jan's chromatogram shows a pattern similar to that of the urine, with strong glutamic acid, glycine, glutamine, lysine, alanine and valine spots, and moderate leucine, phenylalanine, tyrosine and serine spots. . . . The total pattern is definitely stronger than that given by a like quantity of normal plasma. Nevertheless, these plasma results should be treated with caution, as the plasma may have been partially decomposed after so long a journey. Microbiological assays on another specimen of Jan's plasma were done, and the aminoacids tryptophane, phenylalanine, valine, tyrosine and arginine found to be present in normal or low quantities.'

Summary

The object of this paper is to review the present position of the various syndromes resulting from innate defects of renal tubular function, with particular reference to certain patients of our own. The first patient was a boy of 10 years with hypophosphataemic glycosuric rickets and infantilism, albuminuria, hypocaturia, and reduced production of ammonia in response to acid stress. His renal phosphate clearance was high. He showed considerable reduction of glomerular function. He was mentally backward and deaf-mute, and showed a gross pigmentary retinal degeneration. His sister, who resembled him in general appearance, had the same aural and ocular conditions, and showed similar biochemical abnormalities to a much smaller degree. She had neither hypophosphataemia, glucosuria, nor rickets, but there was sufficient evidence for her to be classed with her brother as an example of multiple innate deficiency of renal tubular function. In both children a slight increase in urinary aminoacid excretion was shown by two-way chromatograms and microbiological assay.

The rachitic changes in the first patient responded well to massive doses of vitamin D, and the effect of the vitamin on phosphate retention and on calcium excretion is considered.

The third patient was a girl of 13 years with glycosuric rickets, osteoporosis, and infantilism. Her organic-acid and aminoacid excretion was much increased above normal, and her ammonia production defective. Her serum-phosphorus was usually very low, but two remarkably high values were found in the earliest investigations. She had a marked polyuria, unresponsive to pitressin. She also suffered from typical retinitis pigmentosa. Her sister (Case 4) also had severe retinitis pigmentosa, and almost certainly suffered from the same (Fanconi) type of renal tubular deficiency, from which she died at the age of 22 years.

After a consideration of these cases and of some details of their acid-base balance and acid elimination, the general group of innate tubular deficiencies is discussed. As far as we know at present this group includes the multifactorial defects—the Fanconi and similar syndromes—and the unifactorial defects—hyperchloraemic nephrocalcinosis, renal diabetes insipidus, pseudohypoparathyroidism, vitamin-D resistant rickets, renal glucosuria, ‘classical’ cystinuria, Wilson’s disease, idiopathic hypercalcuria, and possibly galactosaemia.

Finally the genetic characteristics of this group of syndromes are briefly reviewed. Our own cases suggest a hitherto undescribed recessive gene-complex producing multiple renal tubular deficiencies and retinal degeneration; deaf-mutism appeared also in one family.

ADDENDUM

Another case of congenital deaf-mutism, pigmentary retinal degeneration, and a renal tubular defect, has recently been seen in the Paediatric Department. The patient was a girl aged four years who had nephrotic nephritis following an acute nephritis nine months before. She developed tetany with low serum-

calcium, but was not rachitic, and did not pass excessive amounts of amino-acids. She had a constant renal glycosuria (with normal glucose tolerance) which we believe represents her congenital tubular abnormality, as it is not a feature of nephrosis. The nephritis appears to be incidental. Cystinosis was not found at autopsy.

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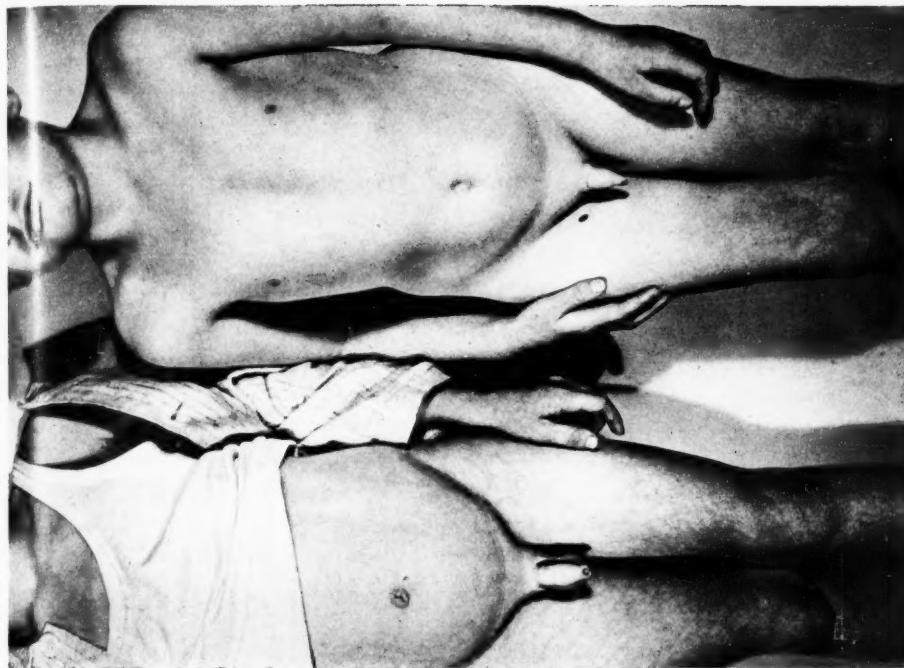


FIG. 3. Showing Jan's skeletal and sexual infantilism. A normal child of the same age on the left

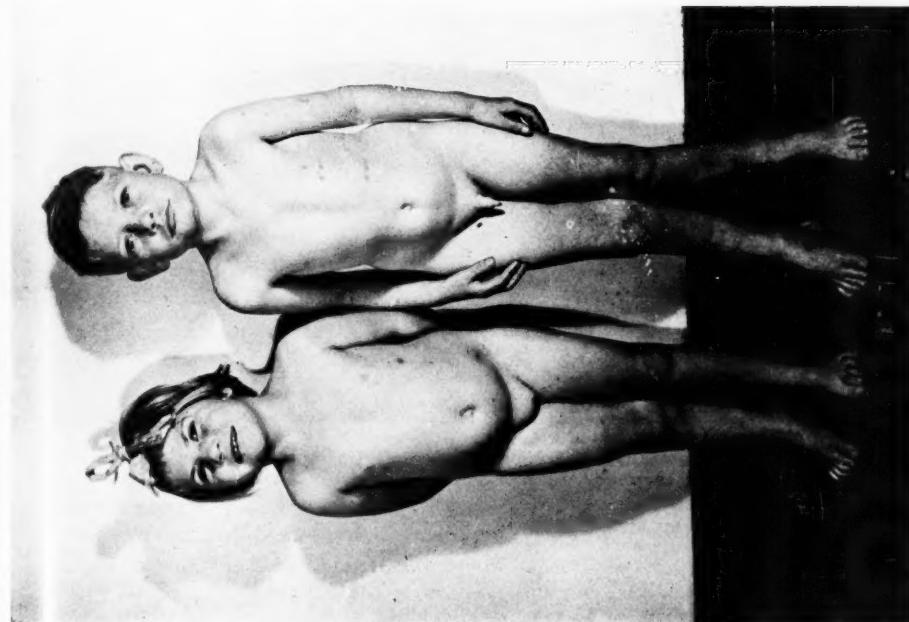


FIG. 2. (Cases 1 and 2) Jan and Anna



FIG. 4. Jan's hand (October 1950) with a control of the same age on the right



FIG. 5. Jan's hand (May 1951) on the left, showing little change from Fig. 4. The X-ray on the right shows the striking effect of vitamin D after 10 weeks

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INCLUSION ENCEPHALITIS AND ITS RELATION TO SUBACUTE SCLEROSING LEUCOENCEPHALITIS¹

A Report of Five Cases

By JOHN FOLEY and DENIS WILLIAMS

(From St. George's Hospital, London)

With Plates 14 to 17

VIRUS diseases of the nervous system usually run an acute course, and although it is recognized that the sequelae of Type A encephalitis may be due to continuing infection, it is only in recent years that we have come to suspect that a virus infection can produce a subacute or chronic progressive condition. The recognition by Dawson (1933, 1934) of subacute inclusion encephalitis, and the description by van Bogaert (1945) of the closely similar condition, subacute sclerosing leucoencephalitis, have made it clear that these conditions, which on histological grounds are almost certainly of virus origin, may run a course which in many respects resembles that of other progressive diseases which have hitherto been regarded as degenerative. The close resemblance, both clinical and pathological, between these two forms of encephalitis has been pointed out by Greenfield (1950). It may well be, therefore, that subacute virus infections of the nervous system may have much greater importance than is inferred from their rarity. Five cases of subacute inclusion encephalitis are reported in the present paper. They are of interest for a number of reasons. First, they were all recognized during life, and were consequently studied in some detail; secondly, their clinical course ranged from relatively acute to chronic, the fifth case suggesting that the disease may become arrested; and thirdly, they demonstrate that this condition, hitherto regarded as predominantly polioclastic, may involve the white matter extensively, thus bridging the gap between inclusion encephalitis and subacute sclerosing leucoencephalitis.

Case Reports

Case 1 (St. George's Hospital, No. 144757). P. G., a boy aged 10 years. Duration of illness 27 weeks. *Onset with intellectual impairment, confusion, petit mal, and akinetic attacks, followed by tremor of hands and myoclonic jerks. Hypokinesia, mutism, periodic involuntary movements, increasing rigidity, and finally decortication; persistent systemic hypertension. Typical changes in cerebrospinal fluid and electroencephalogram.*

This patient was the child of healthy parents, and his younger brother is well. He spent his childhood in India, and apart from malaria at the age of 3 years, pertussis, and varicella, he had been in good health. His development and intelligence had been normal. There was no known contact with any similar

¹ Received July 9, 1952.

case, or with any sick animal. He returned from India two months before the onset of his illness, and lived in Dorset.

Nine weeks before admission he became less interested in his work at school, his speech and movements became slow, he dropped things, and a slight tremor of the hands was noticed. He was once found wandering round the school grounds, having forgotten to go home; and on one occasion he forgot to get off the bus on the way home. *Seven weeks before admission* he suddenly vomited; thereafter he would occasionally vomit, sometimes in his sleep. About this time sudden drops of the head were observed, with relaxation and closure of the eyes, the bout lasting a fraction of a second; these attacks often interrupted speech, and soon they happened five or six times an evening. *Six weeks before admission* he had a generalized convulsion. On the following day he had another fit, and on the next day a third. After this, trembling and clumsiness of his fingers became obvious, and gradually the muscular jumps and jerks, which were so obvious on admission, made their appearance. Five days after the third fit he was found 'crying hysterically' in his sleep, and eight days after the first fit he is again described as having been hysterical. A further fit was followed by difficulty in talking and swallowing. His walking was unsteady; in spite of the tremor of his hands he could feed himself. His appetite began to decline. There was no excessive thirst, no enuresis, and no change in the sleep rhythm. *Four and a half weeks before admission* to St. George's Hospital he was admitted to the Royal Portsmouth Hospital. He had no fever, and was well nourished. Speech was slow and stuttering. His ocular fundi were normal. He had a left internal squint; there was no nystagmus. There were no abnormal signs in the arms, but the legs were slightly spastic, with ankle clonus on the left. Stiffness of the neck and a positive Kernig's sign were found in the first week. At lumbar puncture the pressure was 130 mm., and the cerebrospinal fluid, including the colloidal gold reaction, was normal. He had a further attack in which he cried, his fingers twitched, and he was described by the nursing staff as hysterical. On 2.3.51 he was seen by Dr. G. S. Graveson, who made a diagnosis of inclusion encephalitis. On 15.3.51 the electroencephalogram showed characteristic changes (see p. 161 and Fig. 1). In the last few days before his transfer he became more drowsy, and vomited several times. He was admitted to the Neurological Unit of St. George's Hospital on 26.3.51.

Condition on admission. He was a well-nourished boy, and on general examination the only abnormalities detected outside the nervous system were rather deep irregular respiration and a blood-pressure of 140/100 without detectable cardiac enlargement; there was no pyrexia. He had no rash, and his mother denied that there had ever been one.

Central nervous system. 1. *Mental state.* Spontaneous movements were strikingly few: he lay in bed usually inert, but would occasionally scratch his nose or smooth his pillow; once only, in the first afternoon, he was observed to put his hand out spontaneously to reach for a toy. In spite of this hypokinesia he was alert, and followed people with his eyes. He seemed interested, but had a rather poor capacity for attention. There was no spontaneous speech, though he would occasionally join in laughter in the ward. Comprehension of speech was slightly impaired. When asked, he gave his name, but otherwise he answered questions in monosyllables; he could not give his address or age. When asked the time he pointed to the ward clock, but could not read it. Asked where he was, he could not answer, and when various suggestions were made he said 'yes' to all of them; when it was remarked that he probably could not say no if he tried he burst into laughter; he did, however, say 'no' when asked to do so. He seemed to recognize common objects, but could not name them; he used a comb and a

tooth-brush, and attempted to get a match out of a box. He recognized his parents, but did not speak to them; when his father, who had flown back from India, entered the room, he cried. He could obey orders in the course of examination, but he often laughed, particularly at his own mistakes. Only after prolonged examination did he begin to cry.

2. *Involuntary movements.* There were frequent extensor jerks, involving the trunk and hips particularly, but they could involve any muscle group: sometimes the eyes would jerk upwards, or there would be a unilateral blink or raising of one eyebrow. Involuntary movements occurred in the arms at approximately regular intervals of eight seconds, and consisted of a sudden jerking abduction of the arms with flexion of the elbows. Similar movements would cause decomposition of a voluntary movement; in doing the finger-nose test, for example, the movement might be carried out in two stages, the hand being placed suddenly on the bed, and the last half of the act being carried out separately, each movement being performed with extraordinary speed and perfect accuracy. Often movements of the limbs were accompanied by a fine, irregular, 'shivery' tremor. There were from time to time athetoid movements of the toes of the left foot. A grasp-reflex was present in both hands and in the right foot. When seizing something with both hands he showed distinct pleasure. There was no sucking reflex. Swallowing of fluids was normal, but solids were often retained in the mouth for some time. He frequently made curious clicking noises in the back of the throat.

3. *Cranial nerves.* There was no visual-field or attention defect; acuity was good, and the fundi were normal. The pupils were moderately dilated, equal, central, and circular, and reacted well to illumination; convergence was never obtained. Apart from a variable left internal strabismus, there were no other abnormalities in the cranial nerves.

4. *Limbs.* Tone was slightly increased in the adductors of the shoulder and flexors of the elbows, while power was good and equal on the two sides. Apart from the fine tremor and the occasional decomposition of voluntary movements already noted, co-ordination was normal. The legs were extended, with both feet slightly inverted and the left hallux dorsiflexed; both limbs were very slightly spastic, but power was unimpaired; co-ordination appeared normal. The deep reflexes were very brisk, but equal, the abdominal reflexes present, and the plantar responses flexor. Sensation was normal throughout.

The results of electroencephalographic and cerebrospinal fluid examinations will be summarized later.

Progress. After two weeks in hospital there had been a slight deterioration in his general condition; he had had two generalized convulsions at night. There was moderate tachycardia, and the arterial hypertension persisted. Fluid intake and output were normal. He was still quite alert, and could give his name and address sometimes. He was never known to speak spontaneously. On rare occasions he would play feebly with a toy, and he would usually reach out for a bright object; usually he lay immobile, merely following people about with his eyes. His nature remained pleasant, and he smiled at his nurses or at any newcomer; but any injection, or attempt at forced feeding, provoked loud and prolonged screaming, and sometimes he would start screaming for no apparent reason. He was doubly incontinent. He slept very deeply at night and, once roused, had difficulty in getting off to sleep again. He rarely slept by day, except for a little in the late afternoon. Periodic jerky movements, at intervals of six to 10 seconds, continued, and might consist of any, or all, of the following: (1) conjugate deviation of the eyes upwards and to the right, lasting a fraction of a second; (2) asymmetrical twitching of the lower facial muscles; (3) sudden

elevation of the shoulders, with abduction of the arms and flexion of the forearms; (4) a sudden forward flexion of the trunk, with deviation always to the right; if held in a sitting position, however, he would jerk backwards; (5) less often, brief flexion of either hip and knee. Apart from a slight right lower facial weakness, there was no alteration in the cranial nerves; convergence was not obtained. There was now a slight and variable plastic rigidity in the upper limbs. Power remained good, but the 'shivery' tremor in movements was prominent; the bilateral grasp-reflex persisted. The tendon-jerks were brisk and equal, the abdominal reflexes were present, and both plantar responses remained flexor.

Six weeks after admission, and 15 weeks after the onset, there was a moderate degree of emaciation, and slight evening pyrexia for which no cause could be found. He lay in a slightly flexed posture, conscious but apathetic; he would look up if called, but would not answer or co-operate, and there was no evidence that he understood speech. The only spontaneous utterance was, once, 'I don't want' when he was washed. He was unable to swallow, and feeding was by tube. His face was expressionless, and his eyes were open, usually deflected to the left, but a blink-reflex was present to threats from either side. He would remove an offending stimulus with a tremulous hand in a sensible way, but would make no effort to prevent himself from being hurt. The periodic involuntary jerking movements were now more stereotyped, and occurred regularly at five-second intervals. In these movements, on a background of slight extension of the trunk, the shoulders were elevated, the arms abducted by a few degrees, the elbows and wrists flexed, and the hips and knees slightly flexed, the whole movement taking from one-third to half a second from start to relaxation. The eyes did not participate, but there was sometimes a slight click in the pharynx. The movements were made more vigorous, though not more frequent, by disturbance, and one hand might then fly up and strike his face. At this stage of the illness a curious response to stimulation was observed, which we have termed the 'echo phenomenon'. Painful stimulation, as opposed to mere disturbance, would modify the involuntary movements in a distinctive way. There would be no reaction after stimulation until an involuntary movement was due. The movements would then be of much greater amplitude, associated with whining and a grimace of pain and anger. Though the stimulus had ceased, the whole of this pattern was repeated five seconds later, the jerk being more vigorous than before stimulation, and accompanied by the same grimace and the same whine. It was as if the response to pain had been grafted on to the pattern of involuntary movements. Several such 'echoes' occurred at intervals of five seconds, becoming fainter and fainter until, after about five or six, only the original pattern of periodic movement was seen. These 'echoes' were sufficiently consistent to be filmed. Their pattern varied from time to time, but was always, at a given time, the same as the initial response to stimulation.

In the fourth month of the illness tachycardia increased, the temperature slowly rose, and the blood-pressure had risen to 200/150; sweating was profuse. The posture was now one of extension of the neck, flexion of the arms, and moderate extension of the legs. The hypertonus was still of plastic quality in the arms, though definitely spastic in the legs. The grasp-reflex was absent, and the plantar responses were extensor. Tonic neck reflexes were absent. There appeared to be a right hemianalgesia. He was inaccessible to speech. His face was expressionless, and blinking was infrequent; the eyes were wide open, deflected to the left, with a coarse nystagmus. The rhythmic movements of the trunk and limbs still occurred at intervals of five seconds, but were much feebler, and in the legs they were only perceptible in the right quadriceps and

hamstrings; in the arms they were accompanied by a fine, rapid tremor. To this picture were added periods of hyperpnoea, with tachycardia of 160 to 200 a minute, and increasing cachexia; death occurred in hyperpyrexia after an illness lasting 27 weeks.

Investigations. 1. *Cerebrospinal fluid.* Ten weeks after onset (lumbar puncture, child restless): pressure 300 mm.; red cells 10 per c.mm.; white cells less than 5 per c.mm.; protein 25 mg. per 100 ml.; sugar normal; chloride 760 mg. per 100 ml.; Lange reaction 5521000000. Twenty-two weeks after onset (lumbar puncture): pressure 125 mm.; red cells 25, white cells less than 5 per c.mm.; protein 49 mg. per 100 ml.; Lange reaction 3210000000.

2. *Electroencephalography.* *Seven weeks after onset*, at the Royal Portsmouth Hospital (Dr. E. Mellor): 'The dominant feature is the presence of a very slow "spike", followed in about 0·1 second by a slow large wave of a frequency about 1½ per second. This combination has an amplitude of about 600–800 microvolts in the frontal areas, and somewhat less elsewhere. The combination is followed by waves becoming smaller in amplitude and faster in frequency (range 2 to 5 per second). The whole of this pattern is followed by a period of relative quiescence, and the cycle is again repeated after an interval of four to eight seconds. In addition, phase reversal occurs in the left frontal area. All the above frequencies partake in this phase reversal. Conclusion: this picture has many features compatible with both acute encephalitis and a subacute type (e.g. of van Bogaert)' (Figs. 1a and 1b). *Nine weeks after onset*: in this record, taken with normal amplification, the general pattern was one of approximately symmetrical 2½-, 4½-, and 7-per-second activity; but faster rhythms at 19 per second were also in evidence, particularly in the left frontal lobe; in addition there were occasional sharp spikes in both frontal areas. This pattern was interrupted at intervals of five to 12 seconds by periodic complexes consisting of two to five slow spikes followed by a high-voltage slow wave and then a brief period of relative quiescence (Fig. 2). The exact pattern of these complexes varied considerably, but they were clearly distinguishable from the general basal activity. Shutting and opening the eyes had no effect on the general activity or on the periodic complexes, while overbreathing merely eliminated most of the fast activity. *Fourteen weeks after onset* there was a general diminution of the faster frequencies, and the complexes had undergone a considerable simplification (Fig. 3). They now occurred more regularly, at intervals of five to six seconds.

3. *Serological tests.* The following tests gave negative results: neutralization and complement fixation tests for herpes simplex, complement fixation tests for the virus of lymphocytic choriomeningitis, Coxsackie virus, and influenza A and B virus, and agglutination tests for leptospirae.

4. *Miscellaneous tests.* Blood-urea, serum-calcium, and blood-sugar levels were within normal limits. The blood count showed no deviation from normal except a mild polymorphonuclear leucocytosis towards the end of the illness. The Wassermann and Kahn reactions were negative. The urine was normal, and contained no excess of porphyrins.

Treatment. Courses of aureomycin by mouth and intravenous injection, chloramphenicol suppositories, and penicillin had no effect on the disease; phenytoin, troxidone, and paraldehyde did not influence the rhythmic jerking movements.

Autopsy. Apart from a moderate degree of cardiac hypertrophy and some fatty change in the liver, abnormalities were confined to the nervous system. After removal of portions for animal inoculation, the brain was hardened in formol-saline and submitted to Dr. J. G. Greenfield, who reported as follows:

'The brain was well fixed in formol-saline solution. No external abnormality

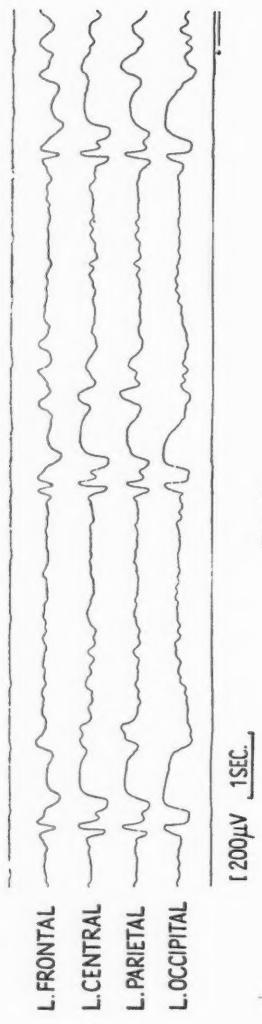


FIG. 1a.

$1200\mu\text{V}$ 1SEC.

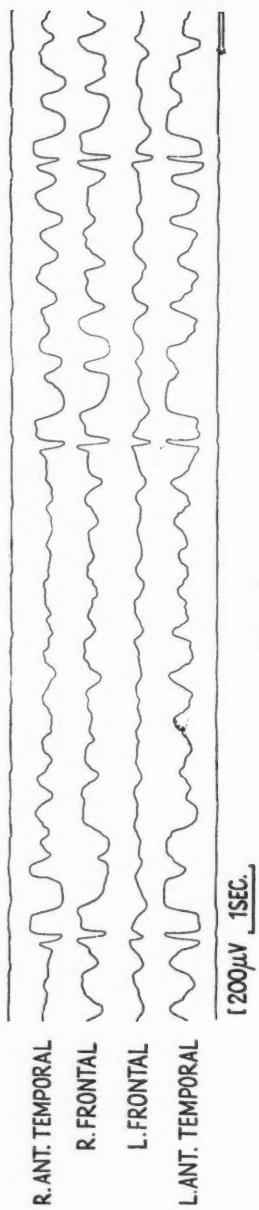


FIG. 1b.

FIG. 1. Case 1. Electroencephalogram seven weeks after the onset.

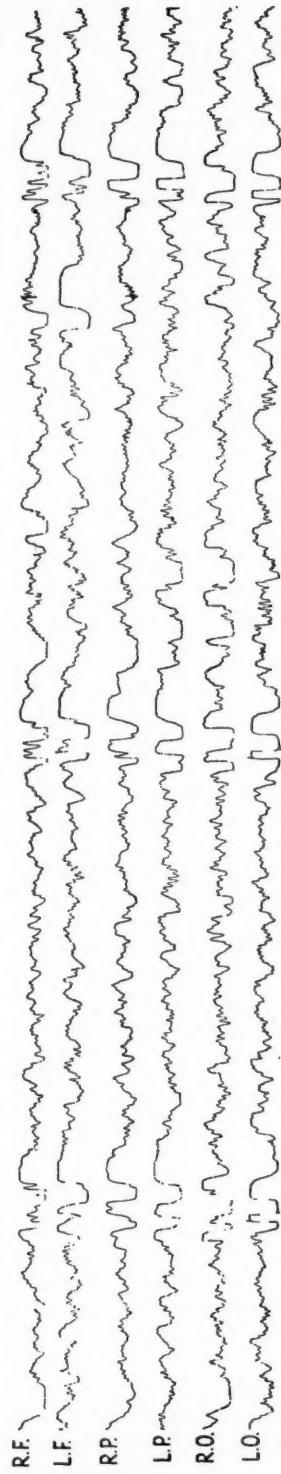
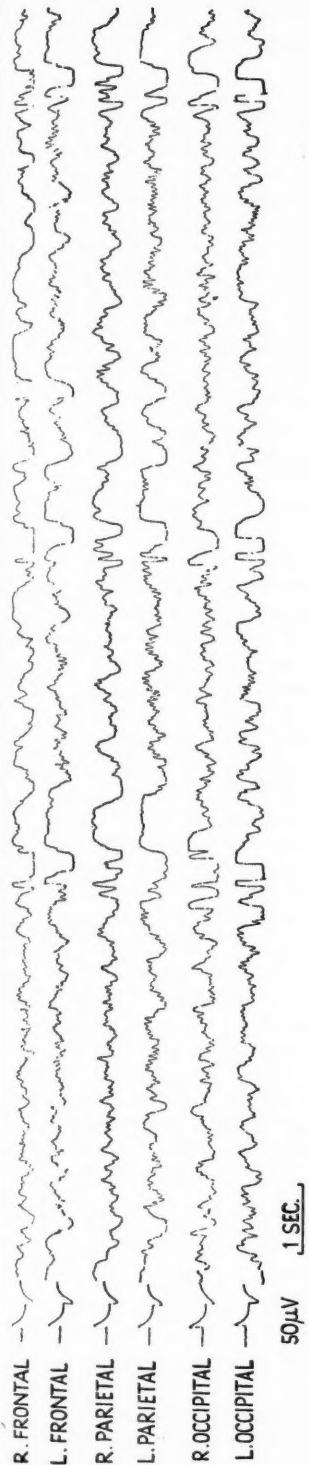


FIG. 2. Case 1. Electroencephalogram nine weeks after the onset.

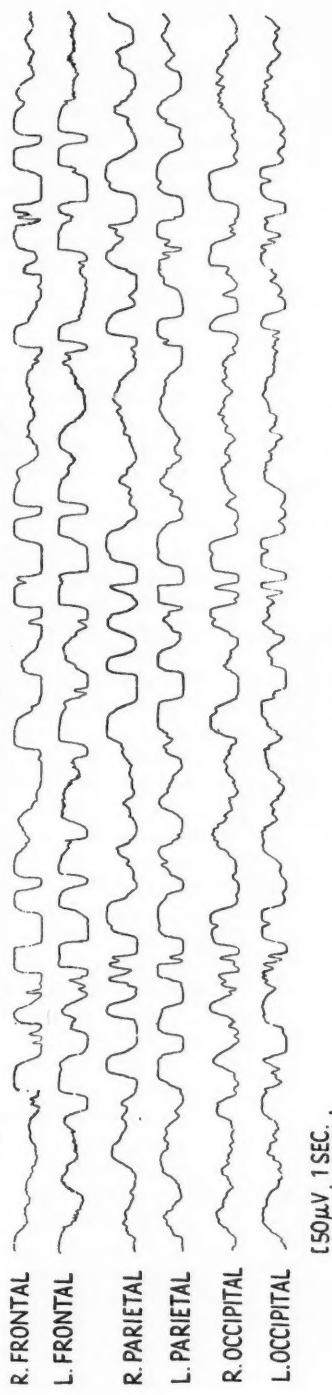


FIG. 3. Case 1. Electroencephalogram 14 weeks after the onset.

was seen. On section of the cerebral hemispheres in the coronal plane, the white matter of the occipital lobes, the upper posterior part of the left parietal lobe, and the whole of the posterior part of the temporal and upper posterior part of the frontal lobe on the right side as far forwards as the head of the caudate nucleus, showed an abnormal creamy texture, like a firm cream cheese, with multiple very small holes. In some places in both occipital lobes the white matter was divided from the cortex by a split, which was certainly artefact due to the abnormal consistency of the white matter. The cortex itself looked rather thin and firm over the area of abnormal white matter, but was not obviously degenerated. No band of more normal U fibres lay anywhere between the cortex and degenerated white matter. Elsewhere no gross abnormality was seen on section. Frozen sections, after embedding in gelatin, of the left occipital lobe, were stained by Scharlach R and haemalum, and paraffin sections of the frontal, temporal, and occipital lobes, of the basal ganglia including the putamen, globus pallidus, and anterior part of the thalamus, and of the pons, were made and stained by haematoxylin-eosin, phosphotungstic-acid haematoxylin, and Lendrum's phloxin-tartrazine stain for inclusion bodies. Several pieces were also taken for celloidin embedding.

'Frozen sections of the left occipital lobe showed the myelin to be almost completely broken down into sudanophil material, which was largely in the form of anisotropic spicules' (Plate 14, Figs. 9 and 10). 'It lay both within fat-granule cells and as fine granules between the cells. The cell-bodies of the astrocytes were much swollen, many contained a few fine sudanophile granules round their margins, and there was a moderate degree of perivascular cuffing by lymphocytes and plasma cells. Paraffin sections showed in the cortex everywhere evidence of subacute inflammation, greatest in the occipital lobes and over the areas of degenerated white matter, and also in the pyramidal layer of the hippocampus, where most of the nerve-cells had disappeared and the astrocytes were more numerous than normal and had swollen cell-bodies. There was gross inflammatory destruction of Sommer's sector of the pyramidal layer of the hippocampus including H.E.2, as well as of H.F., where only swollen astrocytes and microglial cells were seen. Elsewhere in the temporal, and in the frontal lobe, the changes in the cortex were rather mild; there was a variable mobilization of the microglia with rod-cell formation, an occasional double astrocyte nucleus, a few plasma cells free in the tissues, and an occasional cuffed vessel. There was certainly degeneration and disappearance of many nerve-cells, but inclusion bodies were very difficult to find here. In the white matter of the left temporal lobe, although there was no gross demyelination, all the astrocytes had much-swollen cytoplasm and were forming new fibres. This was specially evident in the optic radiations, where the tissue also was rather spongy. Many of the oligodendroglial nuclei contained hyaline phloxinophile inclusions. In the occipital lobes this glial hyperplasia was very prominent and many swollen astrocytes were also seen in the deeper cortical layers, though few of the latter formed fibres. The zone of rarefaction, where the cortex tended to become separated from the white matter, was in the fifth and sixth cortical layers. There was also much gliosis, with swollen fibre-forming astrocytes, in the first and to a lesser extent the second layer. Rod cells were very numerous here, and there was considerable loss of nerve-cells, though many fairly normal cells remained. Inclusion bodies were not numerous here, but especially in the most damaged areas some of the remaining nerve-cells contained typical intranuclear and cytoplasmic inclusions' (Plate 14, Fig. 11).

'The basal ganglia showed little abnormality in the areas examined, except in the lateral nucleus of the thalamus, where there was an area with loss of

nerve-cells, perivascular infiltration, swelling of astrocytes, and mobilization of microglia. A number of oval or rounded hyaline bodies here probably represented the remains of nerve-cells, but the severe "inclusion body" degeneration seen in the thalamus in other previously reported cases was seen in only one nerve-cell. Apart from slight perivascular infiltration on its margins, the substantia nigra showed no changes. The nuclei pontis showed severe inflammatory changes, such as perivascular infiltration and microglial nodules, and here very many of the nerve-cells contained typical intranuclear and cytoplasmic inclusions. In many high-power fields one could see three cells with more or less typical intranuclear inclusions. Many cells contained two or more small intranuclear bodies' (Plate 15, Fig. 12). 'In the tegmentum the only evidence of the disease was an occasional infiltrated vessel.

'Large celloidin sections of the parietal lobe demonstrated well the severe loss of myelin sheaths in the centrum semiovale. Most of these appeared to have broken down into lipid granules. The swelling of astrocytes and the fibrous gliosis were as great as are seen in cases of diffuse cerebral sclerosis of similar duration' (Plate 16, Fig. 13). 'Throughout the basal ganglia there were occasional vessels showing lymphocytic cuffing, and in the thalamus in addition there was a diffuse increase of microglia. At the midbrain level similar but rather less severe inflammatory reactions were seen in the substantia nigra. At the lower levels of the pons the inflammatory reactions in the nuclei pontis were as severe as in the paraffin sections at the mid-level, but intranuclear inclusions were much less easily found. The tegmentum was practically normal. In the medulla a diffuse increase of microglia, with an occasional glial star, was present in the inferior olives. The cerebellar cortex was quite normal, but the nucleus dentatus showed slight focal excess of microglial nuclei.'

Inoculation experiments (Dr. E. Weston Hurst). Suspensions of brain preserved in ice, and also 'concentrates' prepared from washed deposits in the high-speed centrifuge, were inoculated into newly weaned mice, rabbits, guinea-pigs, monkeys (*M. mulatta*) and (on one occasion) developing chick embryos. A virus was isolated from the mice. The early behaviour of this virus was not typical of herpes simplex, but with continued passages the differences partly disappeared. At the sixth mouse passage, and after four mouse and two rabbit testicular passages, the biological behaviour of this virus was very similar to that of known herpes virus, the histological lesions were identical, and both viruses were neutralized to approximately the same extent by an antiherpetic serum produced in rabbits. Moreover, adult mice surviving intracerebral infection with the virus from this patient subsequently resisted intracerebral inoculation of a known herpes simplex virus. The two viruses were, therefore, identical or closely related. The fact that sera from other cases of inclusion encephalitis, tested by Dr. Hurst, failed to neutralize either herpes simplex or the virus from this patient, supports the view that the virus isolated from Case 1 was a contaminant.

Case 2 (St. George's Hospital, No. 139929). B. K., a girl aged 8 years, of Surrey. Duration of illness 17½ months. *Gradual intellectual deterioration; behaviour disorder, akinetic attacks, and later drowsiness. Akinetic mutism, papilloedema, plastic rigidity, periodic involuntary movements, increasing emaciation, and ultimate decortication. Typical findings in cerebrospinal fluid and electroencephalogram.*

This child was born of healthy parents, and had developed normally; she had had measles in infancy, and at the age of three years injured her forehead, and had a small discharging abscess for two months. During the two years preceding

her admission she had repeated attacks of tonsillitis with mild cervical adenitis. At no time had a rash been observed. Seven months before admission she had bilateral otitis media without perforation.

Six months before admission, on returning to school after the otitis, it was noticed that she was not as intelligent or attentive as before. She continued, however, to attend school. *Four months before admission* she had whooping-cough, but made a normal recovery. *Two months before admission* she began to have attacks of sudden limpness of the legs, and would fall to the ground, without any apparent loss of consciousness; she also had head-nodding attacks, especially in the evenings. She had difficulty in feeding herself because of drooping of the head, or jerks of the arm which would throw the cup down. Occasionally her mother noticed that she would stare blankly and not respond. Sometimes when reading aloud, as she often did, she would suddenly stop and then mumble a few meaningless words. Her sleep was disturbed by cough, but she had no nightmares. Her behaviour became difficult, and she had frequent temper tantrums. Her mother complained that she rarely seemed to understand what was said to her, and would not do what she was told without a 'scene'; she became fidgety, and annoyed her parents by swinging on the doors and skipping in the house. *Two weeks before admission* there was a rapid deterioration in her mental state, and she became unable to concentrate. At times her speech was rambling and nonsensical. She said that she could not see the blackboard at school. Falling attacks occurred often. She vomited twice in three days, and had occasional brief headaches and pains over the eyes. There was no fever, but sweating was profuse at night. *Seven days before admission* she awoke at 3 a.m. and wanted to get up; she was mildly confused, but her movements and behaviour were normal. Her general health remained good. *Three days before admission* to St. George's Hospital she was admitted to the Hospital for Sick Children under the care of Dr. W. G. Wyllie; she was disorientated in time and place, with poor powers of concentration. Apart from bilateral chronic papilloedema, with some secondary optic atrophy, there were no other abnormal signs. At night she became restless, and sedatives were required. Two days later she became drowsy, and was transferred to the Neurosurgical Unit of St. George's Hospital under the care of Mr. Wyllie McKissock.

On admission she was a well-developed and well-nourished child, with a small scar on the right forehead, and a pustule on the right leg. Nothing abnormal was found in the heart, lungs, or abdomen, and she had no fever.

Central nervous system. She was in a state of variable stupor, at times answering questions, at others remaining silent; she could read, but not write, and she co-operated in the examination. Later that day she had hallucinations, and said there was a fire at the bottom of her bed. On several nights she became restless and noisy, singing and attempting to get out of bed, though more often her sleep was deep. The cranial nerves were normal except for slight swelling of both optic discs, nystagmus on gazing to the left, and dysphagia, which made tube-feeding necessary. The limbs were hypotonic, and no incoordination or weakness was observed; the deep reflexes were sluggish, and the plantar responses flexor. No sensory loss was found. Her gait was normal. X-rays of the skull showed evidence of raised intracranial pressure, but a ventriculogram was normal. After ventriculography she became drowsy, and occasional convulsive movements in the right arm and leg were noticed.

Two weeks after admission she was transferred to the Neurological Unit. *Mental state:* she was hypokinetic and completely mute; sometimes she would open her eyes and follow people with them, but more often she lay with her eyes closed and her hands neatly folded across her chest. She reacted vigorously to

painful stimuli, pushing the offending object away with a well-organized movement, her hands exhibiting a rapid shivery tremor. Her stupor could be easily interrupted by stimulation, and her response was always an integrated one. No periodic involuntary movements were observed at this stage. *Cranial nerves*: visual acuity was apparently good, and there was no evidence of a field or attention defect. Both disks were swollen and slightly grey. The pupillary reactions were normal both to light and on convergence; there was bilateral ptosis, and some difficulty in conjugate deviation to the left, but no nystagmus. The lower cranial nerves were normal. *Limbs*: there was a bilateral grasp-reflex. Tone was very slightly increased in the extensors of the elbows. The right arm and leg were moved more than the left; movements were tremulous, but her co-operation was too poor for co-ordination to be assessed. The deep reflexes were sluggish, and the left plantar response was extensor. No gross sensory loss was found. She could neither sit nor walk. A slight improvement occurred, and she was for a short while able to take feeds by mouth; five weeks after admission she spoke clearly once to the nursing staff, and for the first and only time asked for, and used, a bed-pan. Thereafter she relapsed into her pristine stupor. Six generalized convulsions occurred in the next month.

Ten weeks after admission, eight and a half months after the onset, involuntary movements were first observed. Her general condition was much the same, and she lay inert for most of the day with half-closed eyelids and an expressionless face; she was not in coma, for her attention could be gained momentarily by visual or auditory stimuli, and she responded to pain in a co-ordinated fashion. Rarely spontaneous movements were made with the hands, which were brought up and carefully folded, again with a highly characteristic 'shivery' tremor. At intervals of 10 to 20 seconds the head jerked back, the eyes rolled upwards, the arms were abducted, and the pronated forearms flexed, the whole episode lasting about a third of a second and being followed by impairment of consciousness for several seconds. Feeding was difficult because she frequently closed her mouth, though it was obvious that she recognized food, and she would reach out for a piece of chocolate. The only notable alteration in the physical signs was the development of an extensor plantar response on the right side; the left foot tended to lie in an equinovarus position, though there was no definite increase of tone. The periodic jerking movements continued, and affected the right side more than the left; sometimes a brief conjugate upward deviation of the eyes would take the place of a jerk. Four and a half months after admission she was taken home.

Six months after her admission, a year after the onset of the disease, she was seen at home. She was well nourished, being diligently fed by her mother. She lay supine, but occasionally turned on to her left side. She was mute, and there was no evidence that she could see. She appeared to hear loud noises. She had a left hemiplegia, and the blink-reflex to threats was absent on the left side. The disks were flat now, with slightly blurred edges, but the pupils reacted normally to light. There was bilateral ptosis, and a slow irregular spontaneous nystagmus to the right. A feeble grasp-reflex was present in the right hand. The complex involuntary movements were still occurring, but now scarcely affected the hemiplegic side. They consisted of conjugate upward deviation of the eyes, opening of the mouth, extension of the head, abduction of the arm and flexion of the forearm, and slight flexion of the right knee. Sometimes the movement in the arm would be more vigorous, the right arm flying up to strike the face. The whole movement would take about a second. Sixteen months after the onset she still presented this picture of decortication, with periodic involuntary movements occurring every eight and a half seconds, and in this

state she remained, with increasing emaciation, until her death from inhalation pneumonia $17\frac{1}{2}$ months after the first intellectual change had become apparent. A post-mortem examination, limited to the head, was carried out at home.

Investigations. 1. *Cerebrospinal fluid.* Nine and a half months after onset (lumbar puncture): initial pressure 230 mm.; cells 5 per c.mm.; protein 65 mg. per 100 ml.; globulin present. Ten and a half months after onset (ventricular puncture): 12 cells (lymphocytes) per c.mm.; protein 10 mg. per 100 ml.; chloride 750 mg. per 100 ml. Sixteen months after onset (lumbar puncture): initial pressure 180 mm. fluid; cells less than 5 per c.mm.; protein 35 mg., sugar 90 mg., chloride 760 mg. per 100 ml.; Lange reaction 5432210000.

2. *Electroencephalography.* Eight and a half months after onset (Fig. 4) the records showed almost continuous high-voltage 1-per-second rhythms, with occasional coupled waves at 4 and 2 per second which were followed by a slower wave, this in turn being followed by a temporary cessation of the rhythmic 1-per-second activity; during this period a moderate amount of 2-, 5-, and 7-a-second activity could be made out. The coupled waves occurred at intervals of five to 25 seconds. In the middle and posterior leads occasional slow spikes were seen. At times the coupled waves would appear in a more organized form, but these highly characteristic complexes did not occur at regular intervals. Thirteen and a half months after the onset the most conspicuous feature was the occurrence, at intervals varying from 3·5 to 7·5 seconds, most often 6·5 seconds, of relatively stereotyped paroxysms consisting of a slow spike, or more often a wave of 100 microvolt amplitude lasting 0·2 to 0·5 second, followed by a slower wave at 2 per second, this in turn being succeeded by a very slow high-voltage undulation. After this paroxysm there was a period of relatively flat tracings, or of irregular slow waves ranging between 1 and 5 per second. The waves making up the paroxysmal complexes showed an inconstant phase reversal in both frontal regions. The alpha rhythm was absent.

3. *Serological tests.* Neutralization tests and complement fixation tests against the virus of herpes simplex were negative on two occasions. Tests for toxoplasmosis were also negative.

4. *Miscellaneous tests.* Examination of the blood showed only a mild polymorphonuclear leucocytosis. The urine was normal.

Treatment. Courses of aureomycin, 250 mg. thrice a day by mouth or by stomach tube, and a prolonged course of chloramphenicol suppositories together with intramuscular penicillin, were without effect on the disease.

Pathological examination (Dr. J. G. Greenfield). 'Coronal sections of the brain showed no gross abnormality except in the occipital lobes. Here on the right side there was an area of softening, amounting to tissue loss, just above and external to the posterior horn of the ventricle, and brownish discolouration extending round the outside of the ventricle towards the occipital pole where, however, the white matter appeared fairly normal. On the left side the condition was similar, but the brownish discolouration had nowhere gone on to tissue loss. It extended to at least 2 cm. from the occipital pole as brownish streaks in the subcortical white matter.'

'*Microscopical examination* (right hemisphere and brain-stem). *White matter.* Coronal sections of the cerebral hemisphere looked grossly normal, except for the areas of demyelination and softening in the white matter of the occipital lobe and above the ventricle in the parieto-occipital region. Behind the posterior horn the area was a broad band about 3 mm. in width and 12 mm. in length, with rounded ends. It began below the U fibres under the calcarine cortex, and passed downwards and outwards. Above the posterior horn the area was irregularly wedge-shaped with a blunted tip, and measured 16 mm. by 12 mm. in its

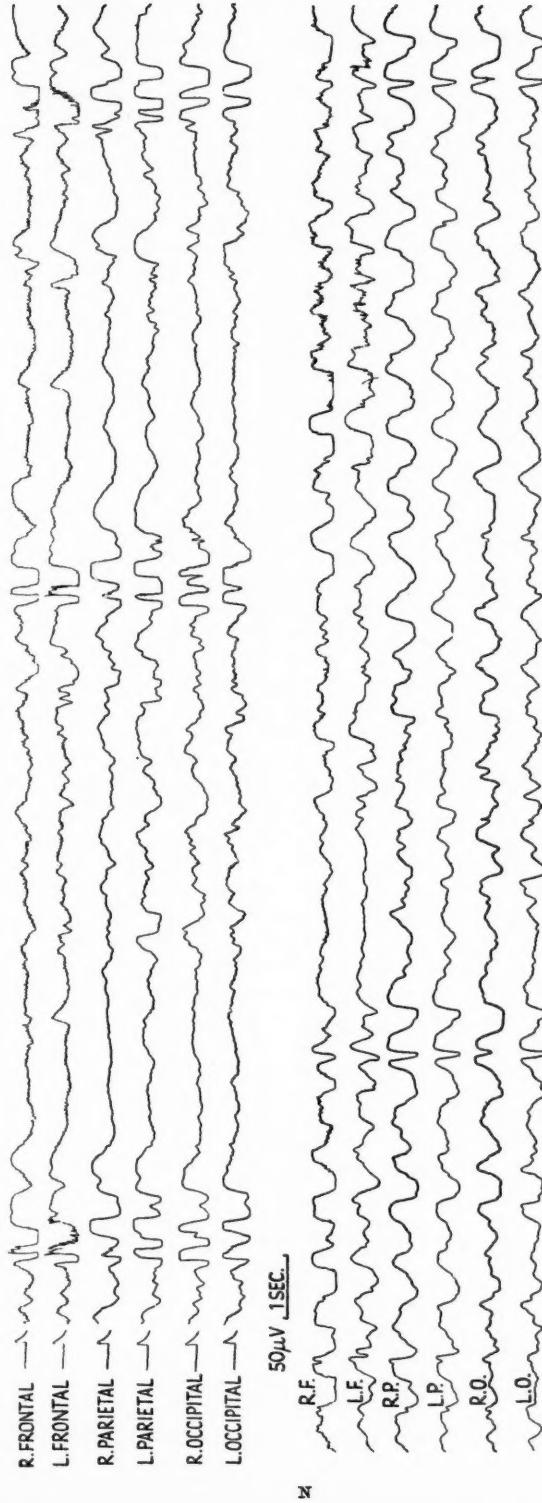


Fig. 4. Case 2. Electroencephalogram eight and a half months after the onset; samples of two recordings made on the same day.

greatest diameters. It consisted here of a zone of complete softening surrounding a less completely demyelinated centre. These areas of softening were separated from the cortex by a zone of intact myelin, which was nowhere less than 2 mm. in width. They appeared to lie external to the optic radiations, which were relatively spared' (Plate 16, Fig. 14). 'In the most softened areas only fat-granule cells and thick-walled blood-vessels were seen, but in many places there were strong neuroglial fibres, sometimes running parallel in bundles, arising from slightly swollen astrocytes. Many of the veins had collections of lymphocytes or cuffs of varying thickness in their walls. An occasional plasma cell was seen free in the tissues, but they were much more sparse than in demyelinated areas in cases of shorter duration. In the less demyelinated zone a few rounded collections of granules, measuring from 20 to 30 μ in diameter, were seen in celloidin sections. The material in them appeared to be closely related to myelin, as it stained black with Loyez-haematoxylin, purple with Mallory's phosphotungstic-acid-haematoxylin, greyish with iron-haematoxylin-van-Gieson, and red with Lendrum's phloxin-tartrazine method. No nuclei could be seen in the majority of these granular masses by the last staining method, by which there was maximal contrast between staining of nuclei and granules. Elsewhere the white matter showed only minor changes. In the zone round the areas of softening, and in some places underlying the more affected areas of cortex, the astrocytes were swollen, and there was some excess of microglia, but no heavily infiltrated areas of white matter were found.

Cortex. The degree of change in the cortex varied from normal to severe necrosis affecting all elements, but the latter was found only in a small focus in the parietal lobe; this may have been a needle track, but it bordered an area with considerable infiltration where inclusions were easier to find than elsewhere. Iron-incrusted nerve-cells were present round its margin. In most areas the changes were comparatively slight. They consisted of degeneration of some of the nerve-cells, which had a darkly stained eccentric nucleus and ragged cytoplasm. The more characteristic form of degeneration, with inclusion bodies in nucleus and cytoplasm, was found only in a very few cells in the more damaged areas of cortex. There were many twins, triplets, and quadruplets of astrocyte nuclei, but the cytoplasm was rarely visible and no fibres were seen in the third, fourth, and fifth layers. The microglia was also increased in moderate degree only. Very few mitoses were seen, and only in a few areas were rod cells abundant, although a few were seen in most areas. Lymphocytic cuffing affected the large cortical veins, and was sometimes quite heavy. An occasional plasma cell lay free in the more affected areas of cortex. No attempt was made to survey the whole cortex, but in general it may be said that the main projection areas of isocortex, such as the pre- and post-central and calcarine, were relatively or completely free of infiltration; the other areas varied without any apparent systematization, but the more posterior areas were more affected than those more anterior; the frontal and temporal poles were relatively spared. The cornu ammonis in this case was relatively intact. Occasional intranuclear and intracytoplasmic inclusions were found in certain occipital, temporal, and parietal areas, all on the external surface of the hemisphere. Most of the intranuclear bodies were small, occupying less than half the area of the nucleus; a few, however, filled the nucleus completely. Cytoplasmic bodies which were strongly phloxinophilic were very scarce. In the occipital lobes a few curious cells were seen, consisting of several more or less rounded hyaline masses, staining orange by Lendrum's method, separated by septa full of chromatin material. These may have been nuclei in which the inclusions had not fused as they usually do. No cytoplasm was seen round them. They were only seen in sections stained

with Lendrum's method. Small glial stars were scattered here and there in the deeper layers of the cortex.

'Basal ganglia and brain-stem. Several small areas of almost complete necrosis were seen in the putamen. Here all the nerve-cells had disappeared, there were numerous fat-granule cells, and a few mitoses in microglia and fat-phagocytes; there was gross loss of astrocytes and oligodendroglia. The capillaries and small vessels here were dilated, and some showed terminal thrombosis. Round this area was a zone of astrocytic reaction with early fibre-formation. No inflammatory infiltration was seen in these areas. The lenticular and caudate nuclei were otherwise almost normal. In the thalamus there were several heavily cuffed vessels and a few loose collections of microglial nuclei, but very little degeneration of nerve-cells. In the corpus Luysii no abnormalities were seen. There was a rather diffuse excess of microglial nuclei in the substantia nigra, but little degeneration of neurones. One or two more focal collections of small nuclei were seen in the tegmentum of the midbrain. Among the nuclei pontis there was intense microglial proliferation and many degenerated nerve-cells, but none was found with cytoplasmic or intranuclear inclusions. Several heavily cuffed vessels were seen here. Only slight changes were seen in the tegmentum pontis. In the medulla, a few rather loose glial stars were seen in the inferior olives. No inclusion bodies were seen in its neurones. Some small glial stars were also seen in relation to the nucleus ambiguus, and an infiltrated vessel was found under the ependyma of the ventricle. In the molecular layer of the cerebellum there was here and there a focal excess of microglia. In one area on the posterior margin there was a definite 'glial shrub' associated with neuronophagy of degenerated Purkinje cells. In the nucleus dentatus there was both diffuse and focal excess of microglia, but little neuronal degeneration.'

Inoculation experiments. Portions of the brain, preserved in ice, were submitted to Dr. F. O. MacCallum, who inoculated suspensions of ground brain intracerebrally into five mice; after four days one mouse died, and suspensions of its brain were injected into five further mice, all of whom, however, remained well. Intracerebral inoculation and corneal scarification in one rabbit caused no ill effects; the suspension was also inoculated on to the chorioallantoic membrane of seven 10-to-12-day old chick embryos, with negative results. Similar inoculation experiments performed by Dr. Weston Hurst also proved negative.

Case 3 (National Hospital, No. 28988). Admitted 26.1.51. C. B., a boy aged 8 years. Duration of illness 14½ months. Disorderly behaviour, intellectual deterioration, dysgraphia, myoclonic jerks, and petit mal. Restless and active, with increasingly frequent involuntary movements, and periodic akinetic attacks when walking. Rigidity of right side; ultimate dementia, with death in hyperpyrexia. Typical changes in cerebrospinal fluid; no striking periodic features in electroencephalogram.

The history was obtained from the child's mother. His father had been killed in the war, and little was known of his father's family. His mother was well, and there was no history of mental or nervous disease in her family, with the exception of her cousin who had died at the age of 25 years of a cerebral tumour. The patient was an only child, and had been born at full term by normal labour after a normal pregnancy. His development was normal up to the time of onset of the present illness; he was above average intelligence.

Nine months before admission his mother gradually became aware of a change in his disposition; he became noisier, and at times rude, having been previously a quiet and well-mannered child. His performance at school began to fall off,

and after six months he had become quite unmanageable and could no longer read, write, or draw. *Three months before admission* he was fidgety, and unable to concentrate on any activity. He could not sit quietly, but would bang his head against the wall, suck his thumbs, and bite buttons off his clothes. He ate chalks, chewed pencils, and ate scraps of food off the floor. He was noisy, slamming doors and shouting at the top of his voice, though apparently not because of temper. He became stubborn and unreasonable, and had to repeat three times over words or phrases commonly used, or acts such as kissing his mother or switching off the light; sometimes he would sit counting from one to ten over and over again. His speech deteriorated and became slurred. About two months before admission involuntary movements were observed for the first time, consisting of a sudden jerk of the arm outwards, making him upset things. Brief attacks also occurred in which his eyes rolled upwards, he became 'blank', and staggered backwards and to the right, without falling. His gait became unsteady. *Six weeks before admission* to the National Hospital he was admitted to St. James' Hospital, Portsmouth, under the care of Dr. E. Sylvia Lendum. He was restless, and ran about the ward, often falling and hurting himself, and he often fell out of bed at night. He chewed his bed-clothes, and once broke his bedside locker and tried to eat the wood. Sometimes he would scream for no apparent reason, and then stop abruptly with a bright smile. His habits were at first clean, though there was frequency of micturition; soon, however, he became incontinent of urine. He became increasingly confused, and had great difficulty in following conversation; often he could not obey instructions, though he could imitate actions if shown. Spontaneous speech was at times scanty, though the nurses reported 'sudden outbursts of conversation, which he shouts at one'. On one day he sang repeatedly one line from a song. When trying to write his name he crossed the 'o' instead of the 't', while 'y' was written as a single stroke. He had slurring dysarthria. There was only slight incoordination of the arms. Myoclonic jerking movements affected the right arm and leg. The deep reflexes were brisk, especially on the right, but both plantar responses were flexor. There was a trunk ataxia, with a tendency to fall backwards and to the right. He was seen by Dr. G. S. Graveson, who made a diagnosis of inclusion encephalitis.

On admission to the National Hospital on 25.1.51 he was a well-developed and well-nourished boy, and nothing abnormal was found on general examination. There was no fever.

Central nervous system. He was confined to his cot, in which he scrambled about like a child of two years, but when asked he would stand up for a few seconds. He shouted with excitement when he saw a dog or a bird in the street outside. Co-operation was slight, and spontaneous speech was limited almost entirely to baby talk, though he would repeat his name, age, and address in a monotonous voice. Speech was slightly slurred. He was left-handed. Shortly after admission he had visual hallucinations at night, consisting apparently of animals. Involuntary movements occurred at intervals of one to two minutes, and consisted of a sudden jerk, which involved almost the entire body. The eyes closed momentarily, the head and trunk sank forwards, the arms were adducted, and the elbows and hips flexed. If standing, he would fall to the floor. He also had attacks of petit mal, in which the eyes rolled up and he would not respond to questions for a few seconds. The cranial nerves showed no abnormality. Likewise nothing abnormal was found in the limbs, though his gait was wide-based and very unsteady, and when he was supported it was interrupted by sudden stumbles to the right, occurring periodically, of which he seemed quite unaware. The deep reflexes were brisk and equal, and the plantar responses

flexor. Two weeks after admission there was some plastic rigidity in the right arm and leg, but there was no change in the reflexes.

A month after admission ventriculography and a right frontal cortical biopsy were performed. He remained active, playing and jumping about in his cot, but his mentality had deteriorated further. The involuntary movements now occurred at intervals usually of four to five seconds, though the periodicity was not constant. Extrapyramidal rigidity in the right half of the body was now more marked. Six weeks after admission the right plantar response was extensor, and his right hemiparesis still more evident, though the hypertonus was still of plastic quality. After two and a half months, approximately a year after the onset, speech was almost unintelligible, but he could still walk with assistance. He was transferred to the Royal South Hants and Southampton Hospital. Mental deterioration continued steadily, he became mute, and could scarcely eat. The involuntary movements continued, and one generalized convulsion occurred in the last month. The temperature gradually rose, and he died on June 5, 1951, 14½ months after the onset. During the three hours before death his temperature was 108·4°, and during this time the involuntary movements ceased and he was quite relaxed.

Investigations. 1. *Cerebrospinal fluid.* Seven months after onset (Royal South Hants and Southampton Hospital): pressure normal; cells 1 per c.mm.; protein 20 mg. per 100 ml.; Lange reaction 5555531000; Wassermann reaction negative. Ten months after onset: pressure normal; cells 1 per c.mm.; protein 35 mg. per 100 ml.; Nonne-Apelt test +; Pandy test ++; Lange reaction 5555432100.

2. *Electroencephalogram.* Eight and a half months after onset (St. James' Hospital, Portsmouth; Dr. E. Mellor): 'The electroencephalogram was done with seconal gr. 2½ because of the failure of the routine recordings. The record is grossly abnormal, and shows (1) a beta asymmetry. This frequency is absent in the left posterior quadrant, while being present simultaneously in the other areas; (2) phase reversal occurs in the left temporo-occipito-parietal area with frequencies of 2 to 3 a second. Conclusion: an area of abnormality is present in the left posterior quadrant. The lesion is probably deep, and there is a possibility of the opposite hemisphere being involved, though to a lesser extent' (Fig. 5). *Nine and a half months after onset* (Dr. W. A. Cobb): 'On the right side there is some alpha rhythm, probably normal at this age, while on the left the normal rhythms are much less obvious. Some fast activity is present in the right frontal region. Some slower activity is present in all areas, but reaches its greatest amplitude and slowness on the left side anteriorly. This left-sided slow activity, although continuous, shows exacerbations which, for the most part, correspond with the movements which recur periodically. The intervals between these outbursts are variable, though of the order of eight seconds. The changes in the electroencephalogram are a run of waves of greater amplitude and slower than the general background, sometimes associated with one or more sharp waves, and on the whole tending to follow a stereotyped pattern' (Fig. 6). 'When an electromyogram is recorded from the right arm, the increased motor activity is seen to occur very early, if not a little before the slow wave'. *Ten months after onset* (Dr. W. A. Cobb) the electroencephalogram had the same general characteristics, but lateralization to the left side was more marked. On the right side there was a considerable amount of normal activity, including runs of fast waves, which was largely absent from the left; and although there were slow waves on the right, their predominance on the left was very great. It was still difficult to recognize any periodicity in the outbursts which occurred. *Eleven months after onset* (Dr. W. A. Cobb) no new features had developed in the electroencephalogram; the greater abnormality remained on the left side, but

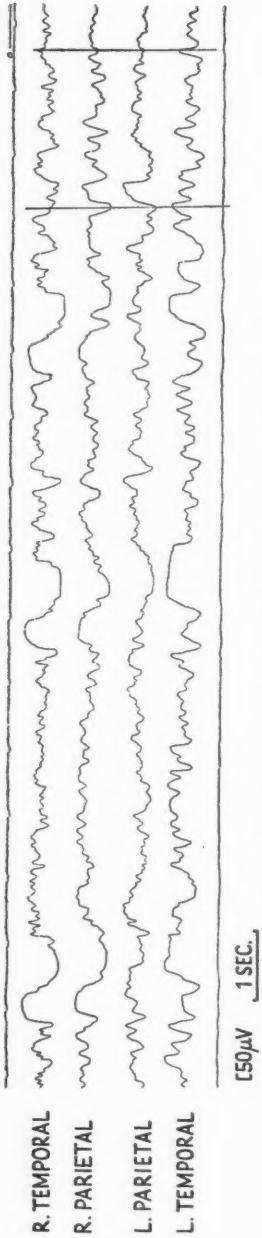


FIG. 5. Case 3. Electroencephalogram eight and a half months after the onset.

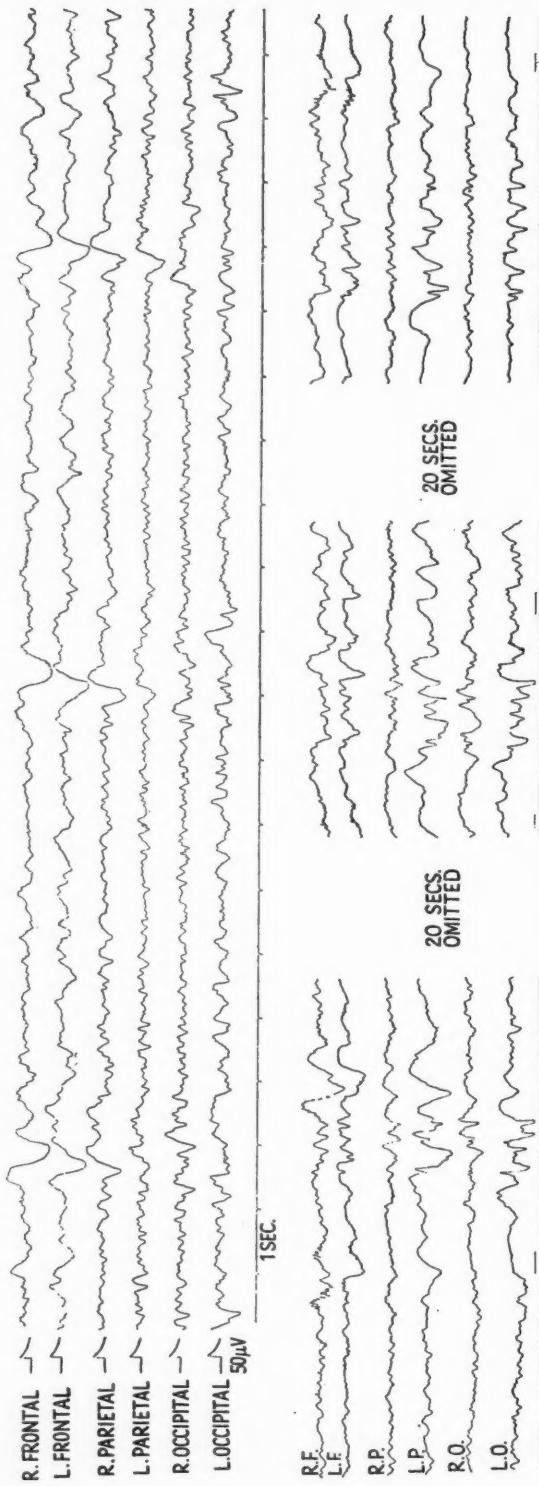


FIG. 6. Case 3. Electroencephalogram nine and a half months after the onset.

any periodicity, if it existed, was masked by the more or less continuous slow activity.

3. *Blood.* Haemoglobin was 90 per cent., white cells were 4,600 per c.mm., with a normal differential count, and the Wassermann and Kahn reactions were negative.

4. *Ventriculogram.* The ventricular system was normal in size, shape, and position.

5. *Right frontal biopsy.* About 1 ml. of cortex and white matter was removed beneath the coronal suture; half was fixed in Zenker's fluid, and the remainder was sent to Dr. Marshall Findlay for injection into animals. Sections of the fixed tissue showed only minor lesions (Dr. J. G. Greenfield). 'The nerve-cells showed no significant change. Round many of the vessels, in both cortex and white matter, there was slight cuffing, chiefly with lymphocytes, and a thicker cuff was seen round the veins. No obvious proliferation either of astrocytes or of microglia was seen in the cortex. In the white matter there was moderate swelling of the cell-bodies of the astrocytes, accompanied by a slight thickening of the fibres passing from these cells, but no diffuse gliosis. There was also both a focal and a diffuse excess of small microglial nuclei, without any evidence of demyelination. These appearances fit into the picture of subacute progressive encephalitis, without either defining its type or being quite specific for this disease.'

6. *Animal inoculation.* Portions of the brain removed at biopsy were injected into the brains of suckling mice without transmitting the disease.

Pathological examination (Dr. J. G. Greenfield). 'No gross abnormality was seen on coronal sections of the brain. Paraffin and frozen sections were made from the prefrontal, temporal (including hippocampus) and occipital areas of cortex, the insular cortex, the body and tail of the caudate nucleus, the thalamus, hypothalamus, and pons. Celloidin sections were made of the basal ganglia, brain stem, cerebellum, and spinal cord.

'Throughout the cortex there was evidence of a moderate inflammation of subacute type, with rod cells, swelling of the cell-body and frequent reduplication of nuclei of the astrocytes, perivascular infiltration with lymphocytes and plasma cells, and occasional plasma cells free in the tissues. The degree of these changes varied considerably from one area to another, and was much the greatest in the hippocampus, which will be described later. In the isocortex they were nowhere more than moderate, and in most places quite slight. An occasional nerve-cell was seen with a fairly typical 'inclusion' type of degeneration: the nucleus was filled with eosinophilic material, leaving a zone of chromophil granules under the nuclear membrane. The cytoplasm of most of these cells also contained flocculent eosinophilic and phloxinophilic material. With Lendrum's method the intranuclear material usually stained orange rather than red, and the cytoplasmic inclusion material varied from orange to red. An occasional cell, apparently a microglial phagocyte, contained granules of phloxinophilic material. The pyramidal layer of the hippocampus was very severely degenerated at its origin in the bight of the fascia dentata, in H.E.2, where very few nerve-cells were left and there were severe microglial, astrocytic, and plasma-cell reactions, with several collections of small nuclei. Especially in this area there were several nerve-cells with intranuclear and intracytoplasmic acidophilic inclusions.'

'Throughout the white matter there was some excess of microglia. All the astrocytes showed slight swelling of their cell-body, and many of the oligodendroglial nuclei had a central acidophilic, rather hyaline, area which might be interpreted as an inclusion. There was little evidence of myelin degeneration in

frozen sections stained with Scharlach R, except in the optic radiations; here, both in the temporal and occipital lobes, there was quite severe degeneration of myelin, with many microglial phagocytes containing isotropic and anisotropic lipid, as well as extracellular deposits' (Plate 17, Fig. 15). 'Elsewhere demyelination was very slight indeed, though deep in the white matter of the frontal lobe there were some scattered, largely extracellular, sudanophilic crystalline deposits.

'In the thalamus there was severe degeneration and loss of nerve-cells, and here the swelling of astrocytes was quite striking. A few nerve-cells with a rounded ball of hyaline acidophilic material replacing the cytoplasm, and a crescentic nucleus usually containing an inclusion, were present. These represented a very late stage in the 'inclusion' type of degeneration of nerve-cells. Frozen sections of the pons stained by Scharlach R and haemalum showed glial nodules and some perivascular infiltration, both in the tegmentum and in the ventral part, but no myelin degeneration.'

'In the celloidin sections an area of partial necrosis was seen in the upper part of the putamen, possibly associated with brain biopsy. Celloidin sections of the midbrain showed an excess of microglia, with rather loose glial stars and perivascular infiltration, but no neuronal lesions. The tegmentum showed much slighter lesions. In the corpora quadrigemina some small veins were infiltrated with lymphocytes. There was a rather diffuse slight microglial proliferation in the nuclei pontis, with hypertrophy of astrocyte nuclei, but no marked change in the neurones. The tegmental region appeared normal. In the medulla there was a focal increase of microglia in the inferior olives, amounting in one or two places to glial stars. The floor of the ventricle appeared normal. The cerebellar cortex was normal; the nucleus dentatus showed changes similar to, but slighter than, those in the inferior olives. No abnormality was found in the cervical or lumbar enlargements of the spinal cord.'

Case 4 (St. George's Hospital, No. 138493). R. M., a boy aged 7 years. Duration of illness six weeks. Brief illness with insomnia, hallucinations, petit mal, and akinetic attacks, leading on to stupor with almost continuous muscular twitching, papilloedema, and slight extrapyramidal rigidity. Typical changes in cerebrospinal fluid; electroencephalographic records not specific.

Apart from the exanthemata the patient had been healthy until six weeks before admission, when he fell out of a tree and was unconscious for about 10 minutes. He then seemed normal, apart from a displaced radial epiphysis. His parents and two siblings were well.

Four and a half weeks before admission his mother noticed that the right side of his face, which was still slightly swollen from the accident, would sometimes become drawn up when he spoke or laughed. *Four weeks before admission* he spent an active day, but refused to go to sleep that night. He sat up most of the time, occasionally lapsing into sleep for a few minutes. Most of the time he sang; sometimes he would stretch out his hand, mostly to the left, and say 'Look, Mummy', though he did not describe what he saw. He also said 'Mum, catch hold of my hand, I am going to cross the road now'. He went to sleep finally at 8.30 next morning, but woke at 10.30 a.m. and wanted to get up. His mother then noticed that he had 'the stumbles': while walking, or when sitting at the table, he would suddenly relax, and his head and trunk would sink; when eating, both hands would suddenly drop. During these drops he did not appear to lose consciousness; he did not fall into his plate, and he never hit the ground. At first these attacks occurred hourly, but they gradually increased both in frequency and severity, so that at the end of seven days the child would flop to the

ground, forwards or backwards, every half minute. No movement of the eyes or twitching of the limbs was seen. In the week after the first restless night sleep-walking occurred twice. *Three weeks before admission* after an akinetic attack he became dazed, was put to bed, and slept two hours. On waking he was mute for an hour, but he then sat up and talked to the doctor, at the same time wetting his bed. He slept well that night, but was kept in bed the next day. He talked and played normally, and no unsteadiness of the hands was observed. Next day he got up, and his gait was normal: there were no more 'stumbles'. His mother was quite emphatic that the illness had progressed in several stages. He was by now noticeably childish; whereas he had previously been the boss, he now fell in with all the suggestions of his sister aged four years, who dominated him with ease. *Two and a half weeks before admission* he attended the fracture clinic; he was thoroughly mischievous and silly, running about, opening doors, and pulling at people's clothes; in the words of his mother he 'talked mental', and he had lost his memory; he was unable to give his name or address. He appeared to understand speech. When told his name was Reggie, he called everything Reggie. Irregular movements of the hands and face were noticed. *Eleven days before admission* he began to vomit in the morning, and did so for three successive days. On the first of these days he fell asleep at 8.30 a.m., and had to be roused at 3.15 p.m. because his parents feared he was in coma; but when roused he seemed much brighter, and his speech was sensible. Next day, however, he could again say little but 'Reggie'. When his father asked him to blow out a match, he merely said 'blow, blow', and did not seem to understand what to do until he was shown. He was admitted to Poole General Hospital, where he was found to show almost continuous twitching movements of the face, trunk, and both arms, absent during sleep. He had attacks, lasting one to two seconds, and occurring in runs at half-minute intervals, in which the eyes would be turned to the left, the eyelids would droop, the head would drop backwards, and the legs would sag; during these his grasp was not relaxed. There were no abnormalities on examination of the nervous system, except for a little blurring of the margins of the optic disks. At lumbar puncture, however, the pressure was 300 mm.; apart from a 'paretic' Lange reaction the cerebrospinal fluid was normal. He was seen by Dr. G. S. Graveson, who made a diagnosis of subacute encephalitis. Two days before transfer he became stuporose; there was only slight twitching of the face. Lumbar puncture was repeated, with the same result.

On admission to the Neurosurgical Unit of St. George's Hospital he was stuporose, inaccessible to speech, but actively resisting all stimuli. If left alone he would lie quietly except for almost universal muscular twitching, which did not resemble the convulsive movements of a fit. The eyes moved to and fro beneath half-closed lids, and the ptosis was more marked on the right. There was bilateral acute papilloedema. The pupils were central and circular, varying rapidly from moderate constriction to complete dilatation; they reacted well to light; occasionally the right pupil was larger than the left. The lower facial muscles exhibited vermicular twitching movements on both sides, and similar movements affected the arms, especially the proximal muscles. The hands, when moved, showed a gross tremulous incoordination. The legs were in an extended posture, but tone was normal. All the deep reflexes were present and equal; there were frequent spontaneous extensor movements of the toes, and both plantar responses were extensor. A ventriculogram was normal, and he was transferred to the Neurological Unit. When seen again five hours later, no abnormalities were found on general examination; pulse and temperature were normal, but respiration was irregular, with occasional sighs and halts.

Central nervous system. 1. *Mental state.* His eyes were usually closed, but

occasionally he opened them and appeared to look around, as he lay supine with his hands folded across his chest and his legs extended. He gave the impression that he could see and hear, and occasionally his eyes would follow a moving object for a few degrees. He responded vigorously to pin-pricks, not merely rubbing the part, but with a tremulous hand pushing the pin away, whining at the same time. When he was asked to sit up and his arms were pulled gently forwards, he seemed to make a real attempt to co-operate, and rose to a half-sitting position. This position would be held for a few seconds, but then tone would suddenly be dissolved in his neck- and trunk-muscles, and he would fall back; after a further two seconds or so he would again attempt to raise his head; several such akinetic attacks, occurring in a person already stuporose, were observed.

2. *Involuntary movements.* Continuous irregular tremors occurred on both sides of the face, affecting especially the lips and eyebrows. Sometimes the upper lip was retracted as if in sniffing, or a grimace was made as though he had something irritating in his nostrils. There were also frequent chewing movements. He occasionally clasped his hands together on his chest as if in prayer, with tremulous jerky movements; this tremor became more coarse in movements of greater extent. In both arms and legs there were frequent irregular twitches, affecting all muscle groups. No involuntary movements were seen in the abdominal muscles. The legs were extended, with the feet in an equinovarus position, and from time to time slight torsion of either limb occurred, while the toes were often dorsiflexed for a few seconds.

3. *Cranial nerves.* He responded to visual threats from either side. Papilloedema was marked, though without haemorrhages or exudates. The pupils were moderately dilated, the right being slightly the larger, and they reacted briskly to light. There was bilateral ptosis. Roving conjugate ocular movements occurred, most often to the right, and at times there was opsoclonia. The corneal reflexes were brisk, and he responded quickly to pin-pricks and tickle on his face. There was no facial weakness. He could hear on both sides, and nothing abnormal was found in the lower cranial nerves. There was slight stiffness of the neck, and Kernig's sign was positive.

4. *Limbs.* On formal testing, tone appeared to be slightly increased in the extensor groups of the upper limbs, in spite of their posture. Power could not be assessed, but sometimes the left arm, if placed in an extended position, would respond to a push with a still more vigorous extension. The tremor has already been mentioned. Tone was normal in the lower limbs, and power could not be assessed. The deep reflexes were sluggish but equal, the abdominal reflexes absent, and both plantar responses extensor. He responded to pin-pricks on both sides of the body.

In the ensuing days there were no changes in the physical signs, and the twitching movements continued; none of these, however, seemed periodic. His state of consciousness declined, while pulse and temperature rose in spite of the administration of aureomycin and penicillin. He died suddenly nine days after admission.

Investigations. 1. *Cerebrospinal fluid.* Three and a half weeks after onset (lumbar puncture): pressure 300 mm.; no cells; protein 25 mg. per 100 ml.; no increase of globulin; sugar normal; chloride 780 mg. per 100 ml.; Lange reaction 4432100000. Four and a half weeks after onset (lumbar puncture): pressure over 600 mm.; cells 22 per c.mm., polymorphs and lymphocytes in equal proportions; protein 25 mg. per 100 ml.; sugar 70 mg. per 100 ml.; chloride 700 mg. per 100 ml.; culture sterile. Five weeks after onset (lumbar puncture): pressure 260 mm.; cells, 12 lymphocytes per c.mm.; protein 55 mg. per 100 ml.; globulin, a trace; sugar normal; chloride 700 mg. per 100 ml. Six

weeks after onset (ventricular fluid): red cells 8,000 per c.mm.; white cells, 40 lymphocytes per c.mm.; protein 85 mg. per 100 ml.; globulin present.

2. *Electroencephalography.* The electroencephalogram five weeks after the onset was very abnormal. The changes were widespread throughout the hemispheres, but showed no specific features. High-voltage slow waves, varying from $\frac{1}{2}$ to 3 a second, occurred in all areas except the right occipital. In the left occipital area they were of lower voltage than in the parietal and frontal areas. None of the periodic wave-complexes described in other cases was seen (Fig. 7).

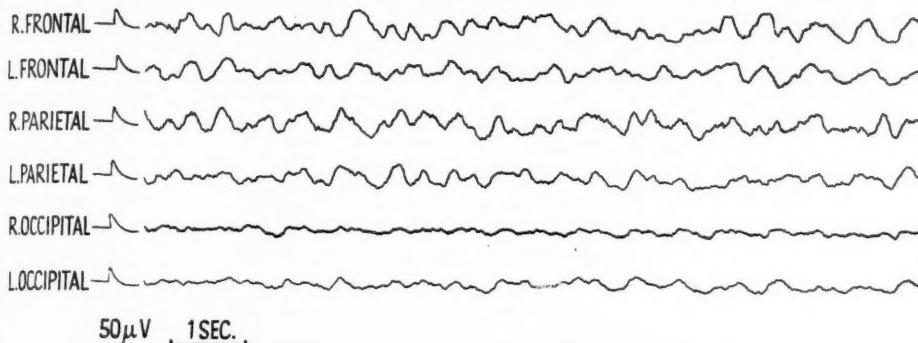


FIG. 7. Case 4. Electroencephalogram five weeks after the onset.

3. *Serological tests.* Neutralization and complement fixation tests for herpes simplex were negative.

Pathological examination (Professor Theodore Crawford and Dr. J. G. Greenfield). No abnormalities were found except in the intracranial contents. There was considerable engorgement of the meninges; the convolutions were slightly flattened, and on section of the brain in the unfix'd state there was slight symmetrical dilatation of the ventricles. Engorgement was evident throughout the brain, especially in the basal ganglia, midbrain, and pons, in which areas the grey matter had a slightly pink tinge.

Microscopical examination of the inferior frontal cortex showed some lymphocytic plugs in small vessels; there was hyperplasia of some microglial cells, but little evidence of increase in their number. In other areas of the cortex the changes were also slight, but there were areas of focal, and more diffuse, proliferation and hypertrophy of microglia. Some plasma cells were seen, both round vessels and free in the tissues. The proportion of degenerated to normal nerve-cells was very small, but in many places the grouping of microglial nuclei suggested neuronophagy. In one section, stained with haematoxylin and eosin, one pyramidal cell was seen containing a small acidophilic inclusion and some eosinophilic hyaline masses near the margin of the cytoplasm (Plate 17, Fig. 16). In the anterior part of the caudate nucleus and putamen, some vessels were heavily cuffed with lymphocytes, but no other abnormality was seen. Sections of the globus pallidus and thalamus were unfortunately not available. In the pons there was excess of microglia in the nuclei pontis, in some places rather diffuse, in others focal, with fairly dense glial clusters; there was slight perivascular cuffing. In the tegmentum there was a very slight excess of microglia. There was no evident change in the nerve-cells of the nuclei pontis, and no inclusions were seen in them. In the medulla there was a very slight excess of microglia in relation to one eighth-nerve nucleus, and glial clusters were seen

round one tenth-nerve nucleus. There was an excess of microglial nuclei in the inner part of the medullary olive, but no dense glial clusters or stars were seen. A vein under the floor of the fourth ventricle showed cuffing with lymphocytes. Complete histological examination was not possible, as much of the material was lost; but the changes seen were in general similar to those found in other cases of subacute progressive encephalitis. Since inclusion bodies may be scarce even in brains showing severe involvement, and only a partial examination could be made, it is not surprising that it was not possible to be certain of their presence in this case, in which no sections were made of very abnormal areas of cortex.

Inoculation experiments (Dr. F. O. MacCallum). Suspensions of parts of the pons and basal ganglia, preserved in glycerol-saline, were inoculated intracerebrally into five mice, intracerebrally and on to the cornea of one rabbit, and on to 10-day chick-embryo chorioallantoic membrane, with negative results.

The fifth case is important because the course has been chronic, the condition being now stationary in its fourth year. The patient came into our hands for further study in the third year of his illness, after a search had been made through our electroencephalographic records for tracings similar to those reported in cases of subacute progressive encephalitis. The history was compiled from statements by his mother and from the notes of other hospitals.

Case 5 (St. George's Hospital, No. 114762). M. B., a boy aged 7 years. Duration of illness over three and a half years. *Gradual onset with dysarthria, choreiform movements, akinetic attacks, and petit mal; progressive dementia, papilloedema, myoclonic jerks, and initially extrapyramidal rigidity, leading on to a state of total dementia with cortical blindness and spastic quadriplegia, in which condition he survives. Typical changes in the cerebrospinal fluid persist, but the electroencephalographic complexes were not well defined.*

Born at full term after a normal pregnancy and labour, the child came of healthy parents, and his development was normal. There was no family history of epilepsy, mental defect, or congenital abnormalities, and he suffered from no other diseases before the onset of the present illness.

Three years before admission, in the early autumn, he began to stammer slightly, and his speech became indistinct. He became a little clumsy when running, and would cry because he could not keep up with other children; previously he had been an active and nimble child. In the course of weeks his movements became gauche, and he often fell off chairs when he attempted to climb on to them. His doctor thought he had chorea. He remained full of energy, slept and ate well, and never complained of headache. After about four months he began to have attacks several times daily in which, when standing or walking, he would suddenly fall to the ground, where he would lie crying; no loss of consciousness was observed. In eating, the spoon seemed to be suddenly dropped or thrown from his hand. No other involuntary movements were observed by his mother, a poor witness. He became incontinent, the frequency of the falling attacks increased to several in an hour, his hands became unsteady, and in the two weeks before his admission to Queen Mary's Hospital, Carshalton, jerky lateral movements of the head were observed, sometimes associated with sudden abduction of the arms. A detailed account of his mental state and behaviour at this time is not available. Two and a half years before he came under our care he was admitted to Queen Mary's Hospital, Carshalton, where tremor of the outstretched hands, choreiform movements, mental deterioration, and bouts of screaming were noted. There was no fever. He rapidly lost the

power of speech. Two months after his admission a note runs: 'This child has general involuntary movements, especially involving the spine'; and the diagnosis of *dystonia musculorum deformans* was considered. The cerebro-spinal fluid was normal apart from a trace of globulin. He was examined by Dr. Blake Pritchard, who found bilateral papilloedema, but no abnormality of the visual fields or ocular movements; both arms were flexed and the legs extended, though not spastic; the plantar responses were flexor. There were frequent isolated spasms of one or all limbs, always provoked by handling. The condition was regarded as one of '*hydrocephalus*, with marked cortical irritability shown as myoclonic twitchings and one major convulsion'. He was transferred to the Neurosurgical Unit of St. George's Hospital.

On admission to the Neurosurgical Unit he was mute and uncooperative, though able to sit up; there appeared to be marked mental impairment. He made no voluntary movements, but when called responded as though he understood. There was a little stiffness of the neck; the skull was slightly enlarged, and had a cracked-pot note on percussion. Vision for small objects seemed good, the fields appeared normal, but there was bilateral chronic papilloedema. External ocular movements were full, and there was no ptosis or nystagmus. The remaining cranial nerves were normal. The arms were in a position of adduction at the shoulders and flexion at the elbows, with clenched fists. Tone was increased in both upper limbs; power could not be assessed. Irregular twitchings were frequent on both sides, especially the left, and could be evoked by sensory stimuli. The deep reflexes were very brisk, especially in the left arm. The abdominal reflexes were present. The lower limbs, especially the left, were extended and spastic; the knee-jerks were brisk, but the ankle-jerks were not obtained. The right plantar response was flexor, the left equivocal. *The electroencephalogram* (23.4.49) was very abnormal, with almost continuous and generalized high-voltage waves at $1\frac{1}{2}$ to 2 a second, though there were not infrequent slow spikes on both sides. At times there were complexes of two or three waves at $4\frac{1}{2}$ to 5 a second followed by a large wave at $1\frac{1}{2}$ a second, this in turn being succeeded by waves of diminishing amplitude and increasing frequency; these groups of waves recurred at irregular intervals, usually of three and a half to eight seconds. A ventriculogram showed merely slight dilatation of the anterior horns of both lateral ventricles, and he was returned to Queen Mary's Hospital; there frequent rolling eye-movements and chewing movements were noticed.

Four months later both optic disks were pale, he was blind, and episodes of drowsiness with irregular pulse and respiration occurred. The cerebrospinal fluid now contained 75 mg. protein per 100 ml. After a further four months he was, for a while, a little more alert, and could swallow without difficulty; at this time he had a healing primary tuberculous focus in the left lung. The involuntary movements continued. In the course of the next six months his dementia became profound; his posture had now changed, and was 'frog-like', with abducted thighs and flexed legs. He was blind and partly deaf, and there were almost continuous lateral oscillations of the eyes; the pupils reacted sluggishly to light. No voluntary movements were possible. There was no grasp-reflex. While he was awake there were continuous involuntary movements of the head and limbs, variously described as jerky and choreiform. From then onwards the only changes were a further alteration of posture, the legs being once again extended, and a diminution of the amplitude, if not of the frequency, of the twitchings.

He was admitted to the Neurological Department of St. George's Hospital for further study on August 30, 1951. He was a small, thin child, without fever,

adenopathy, or rash; nothing abnormal was found in the heart, lungs, or abdomen; respiration was irregular, though not quickened.

Central nervous system. 1. *Mental state.* He lay without voluntary movements; there were slow irregular chewing movements, and sometimes a broad fatuous grin spread slowly over his face. At infrequent intervals he began to bawl loudly, becoming flushed, though not sweating. Speech was absent, and there was no evidence that he understood, though he responded with a grin to a gentle voice or a pleasant sound. He displayed no interest in metallic sounds, the crinkling of paper, or gentle noises, but a loud bang caused a sudden generalized flexion of all four limbs. The sucking reflex, the grasp-reflex, and tonic neck-reflexes were absent. The skull was of normal size and shape, and there was no stiffness of the neck.

2. *Cranial nerves.* There seemed to be no anosmia, for peppermint caused a brief spell of quietness and slight movements of the alae nasa. There was no evidence of vision; both disks were slightly pale, and the maculae were normal. The pupils were moderately dilated and equal, and reacted sluggishly to light. There was no ptosis. Continuous involuntary movements of the eyes occurred. Most of these were irregular conjugate roving movements to the right, but they were interrupted by sudden deviation upwards and to the left, with slight retraction of the lids and a little elevation of both eyebrows. Of all the involuntary movements in the body these conjugate upward jerks seemed to be the only ones occurring rhythmically. They were timed by two observers, and for a period of three minutes occurred regularly every five and a half to six and a half seconds. No definite correlation could be found between these movements and the movements in the limbs, though sometimes the continuous, fine, irregular tremor of the lower limbs was interrupted before a jerk of the eyes. The remaining cranial nerves were normal, apart from a right facial weakness and occasional myoclonic twitches of either angle of the mouth. The neck was slightly extended, and the head half-turned to the left.

3. *Limbs.* The arms were spastic, adducted at the shoulders, and flexed at the elbows, with the fingers flexed but the thumbs extended and lying outside the palm. A continuous fine, rapid, and irregular tremor affected all groups of muscles; there were also occasional sudden jerks of slight abduction at the shoulders and flexion at the elbows, with a greater excursion on the right side; these jerks showed no definite periodicity. The deep reflexes were very brisk, especially on the left. Pin-pricks appeared to be felt equally on the two sides. The abdominal reflexes were just present. Both legs were spastic in extension, with brisk deep reflexes and extensor plantar responses on both sides, only the right foot being withdrawn on plantar stimulation. There was a fine irregular tremor in all muscle groups; in addition there were frequent movements of flexion or extension of the toes. From time to time an abduction-jerk of the upper limbs was associated with a slight flexion of the right knee. Pin-pricks were resented equally on the two sides.

Lumbar puncture showed a pressure of 250 mm., but the child was restless. The cerebrospinal fluid contained no increase of cells; the protein was 20 mg. per 100 ml., but the colloidal gold curve was 4322100000; the blood Wassermann reaction was negative.

Serological tests for herpes simplex antibody were negative.

The electroencephalogram had changed little, though high-voltage slow waves were rather less in evidence. Complexes similar to those previously recorded still occurred at irregular intervals, usually of five seconds, being followed by a period of relative inactivity (Fig. 8). Air encephalography was not carried out in view of his poor general condition, and permission for a cortical biopsy was

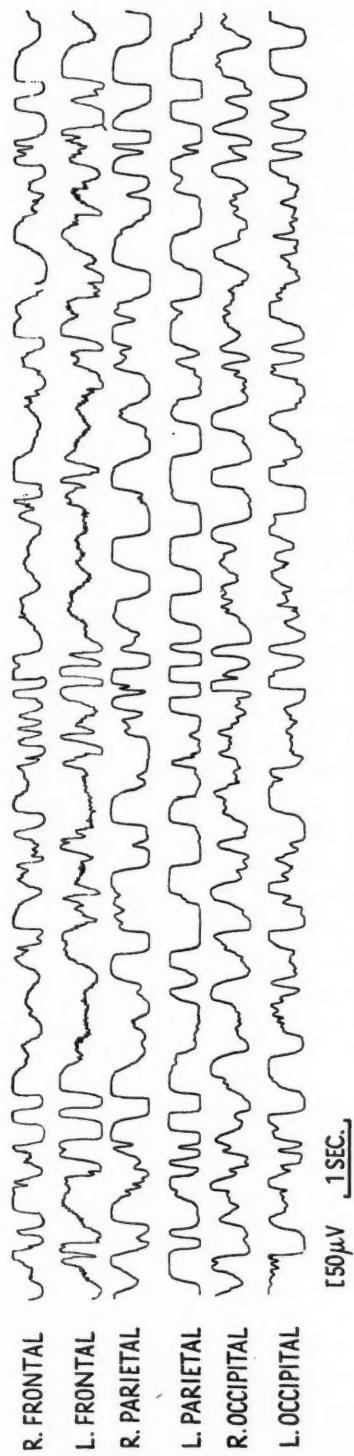


FIG. 8. Case 5. Electroencephalogram three years after the onset.

refused. He was transferred back to Queen Mary's Hospital, and since then his condition has remained unchanged.

In retrospect, the onset with clumsiness of movements, falling attacks, slurred speech, incontinence, mental deterioration, and involuntary movements variously described as choreiform and myoclonic, together with the early papilloedema and later cortical blindness, are compatible with a diagnosis of inclusion encephalitis, as are the electroencephalographic records and the findings in the cerebrospinal fluid. The ultimate state is one of decortication, and differs from that of other forms of cerebral atrophy in that involuntary movements continue and show a faint tendency to rhythmicity. This final state, however, is a non-specific one which could have been due to various destructive processes.

Discussion

Subacute inclusion-body encephalitis was first described by Dawson (1933, 1934), but has only gradually emerged since that time as a clinical entity, apparently distinct from the numerous other instances of subacute encephalitis reported since Type A encephalitis ceased to be an epidemic disease. Cases have been reported by Akelaitis and Zeldis (1942), Brain, Greenfield, and Russell (1948), Malamud, Haymaker, and Pinkerton (1950), Greenfield (1950), and Martin, Macken, and Hess (1950). Meanwhile, however, van Bogaert (1945) had outlined the features of a form of subacute or chronic progressive encephalitis involving principally the white matter, and now known as subacute sclerosing leucoencephalitis, basing his descriptions of its relatively stereotyped features on his own case (described in the paper mentioned), one reported by van Bogaert and de Busscher (1939), the case of Bodechtel and Guttmann (1931), and two more described by Dellaert, Maere, and van Bogaert (1945). Since then cases have been reported by Myle and van Bogaert (1949), Dubois, van Bogaert, and Lhermitte (1949), Macken and Lhermitte (1950), and Corsellis (1951); the cases reported by Hasenjäger and Lenz (1941) and Rosanoff (1947) also belong to this group, as do probably that of Clearkin and Millar (1952), and Case 6 of Bini (1949). Affecting children or adolescents, the course of subacute sclerosing leucoencephalitis is progressive, with intellectual deterioration, behaviour disorders, dysphasia, increasing rigidity with involuntary movements of a choreiform, dystonic or myoclonic nature, and finally a state of decortication. The resemblance of this disease to inclusion encephalitis is so close that in our opinion the two conditions may be regarded as identical. Furthermore, inclusion bodies have since been found in material from the second case of Dubois, van Bogaert, and Lhermitte, and from Case 1 of Macken and Lhermitte (Greenfield, 1952). That the inclusion bodies may be extremely difficult to find in cases of inclusion encephalitis is shown by our Case 2 reported above, in which more than two could never be found in a single high-power field in the most affected areas.

Subacute inclusion encephalitis has up to the present been reported only in the first two decades of life, the youngest patient being just under 5 years and the oldest 20 years of age. No familial examples have occurred, and the sexes have been equally affected. There has been no significant antecedent illness, nor has there in any case been known contact with animals suffering from a virus

disease. It is clear that the condition bears no resemblance to the acute encephalitis occasionally due to the virus of herpes simplex in man. Subacute inclusion-body encephalitis usually runs its course in from two to six months, though in one case (Malamud, Haymaker, and Pinkerton, 1950), in which there were somewhat atypical pathological features, the illness lasted seven years. Case 4 reported above, with a duration of six weeks, appears to be an example of the illness in its most swiftly progressive form. That the disease may not prove fatal is suggested by Case 5, because of the patient's survival necessarily an unverified example, the child being now demented and blind in the fourth year of the illness. Whether the condition can occur in a milder form, from which recovery is possible, is a matter for speculation.

The slowly progressive clinical course may be divided into three stages: the onset with psychic changes, petit mal, and occasional convulsions; the middle stage, characterized most often by a state variously described as stupor or akinetic mutism with extrapyramidal features, and particularly by complex involuntary movements exhibiting a striking periodicity; and the final stage of decortication, the involuntary movements continuing with diminishing amplitude until they are submerged in the ultimate spastic quadriplegia. Even if increased intracranial pressure occurs in the early or middle stages, the nature of the involuntary movements and the quality of the stupor are so characteristic that confusion with cerebral tumours should not occur. General symptoms are inconspicuous, though there is a slowly increasing tachycardia and pyrexia as the illness progresses, while emaciation is attributable to the constant difficulty in feeding. A diffuse rash occurred early in the disease in Dawson's first case (1933), while a herpetic eruption developed 11 days after admission; in his second case (1934) a maculopapular rash of doubtful nature was observed on admission; but otherwise cutaneous eruptions have not been observed. Autonomic signs are also inconspicuous, though glycosuria, bulimia, and polydipsia have been reported, and Case 1 above had systemic hypertension. A persistent reversal of the sleep rhythm does not occur. A remission has been described in only one instance, Case 3 of Malamud, Haymaker, and Pinkerton (1950). The three stages of the disease may now be described in more detail.

1. *The onset.* The earliest symptoms fall into two groups, psychic and epileptic. The earliest occurrence is a change in behaviour and a disintegration of intellect, difficult to detect at first but slowly becoming more evident, with irritability, distractability, temper tantrums, refusal to listen or obey, and deterioration of work at school. In Greenfield's Case 1 (1950) poverty of speech, and a decline in intelligence and all activities, preceded frank symptoms by six or seven months. In adolescents depression or schizoid features may conceal for a time the true nature of the disease (for example, in Case 1 of Malamud, Haymaker, and Pinkerton, 1950). Impoverishment of speech and writing and inability to dress are probably due to the general decline in mental functions, rather than to a specific aphasia or apraxia. Nocturnal enuresis is early, and in the first stage there may occur sleepless nights, and visual, or less often auditory, hallucinations. Convulsions may rarely initiate the illness and punctuate the

course of the disease, but they are never a prominent feature. Far more important are petit mal and akinetic attacks. These usually occur before the emergence of the characteristic, complex, and generally periodic involuntary movements most often, but incorrectly, termed 'myoclonic jerks', but they become less and less evident once the grosser neurological abnormalities have confined the child to bed. Vomiting, especially at night, is an early feature, but does not persist; meningeal signs and symptoms, apart from a little headache from time to time, are not encountered.

2. *The middle stage.* Whereas in the early stage the important features are disorders of habit and behaviour, intellectual deterioration, and epileptic disturbances, chiefly petit mal, the manifestations of the established disease comprise involuntary movements, certain other extrapyramidal signs, and in most cases a poverty of volition greater than can be explained on the basis of dementia, and amounting often to stupor. The intellectual defect is by now obvious, and the child is incapable of dressing or feeding himself. Speech is disturbed in a number of ways, but as a general rule its disintegration runs parallel with the dementia, while its poverty is a reflection of the decline of volitional activity. Aphasia in a pure form is not notable; most commonly slowness, slurring, and interruption lead quickly on to mutism, though a few automatic phrases may be retained. With regard to the level of consciousness, slowness of comprehension, speech, and performance has already been noted. In a few cases there have been alternating periods of restlessness and lethargy, and in Case 3 reported above the patient was active and distractable; but much more striking in the majority is a state of hypokinesis and mutism. The typical lethargy of epidemic encephalitis is not seen, while coma occurs only in the terminal stage. In conjunction with this alteration in responsiveness to external stimuli, in the form of utter indifference, the involuntary movements make up a highly characteristic picture. These movements have, in one or other form, been noted in all but one of the reported cases, and they led Dawson (1933) to describe his first case as an example of the 'amyostatic akinetic' form of encephalitis lethargica. Sudden jerking movements of the limbs occurred in both Dawson's cases and were severe enough in the second to cause injury to the face. A variety of movements has been described, but they may be classed in three main groups.

Most frequently reported have been so-called myoclonic jerks, variously described as 'sudden involuntary flexor jerks', 'intermittent clonic spasms of the flexors', 'constant myoclonic jerks', or merely 'occasional twitching movements of the limbs'. True myoclonus, however, does not seem to occur. Most of these movements are of considerable amplitude, and involve the trunk and one or more of the limbs. They may be mild or violent, but are usually not as abrupt as the misnomer 'myoclonic' implies. In the limbs the movement almost invariably involves the flexor groups, while in the trunk it may be one of flexion or, more often, of extension (sometimes amounting to an opisthotonic spasm), with torsion. Periodic recurrence of such movements, a very important and almost specific feature, has been described by Malamud, Haymaker, and Pinkerton (1950), Greenfield (1950), and Cobb and Hill (1950), though Rader-

mecker (1949) first pointed out the regular rhythmic nature of the electroencephalographic complexes in cases of subacute sclerosing leucoencephalitis. The interval between the movements is most often six seconds, but may be as little as three or as long as 20 seconds. Full descriptions of these movements are given by Greenfield (1950) and by Martin, Macken, and Hess (1950). As the disease progresses the periodicity and rhythm is maintained, but the amplitude becomes restricted by increasing rigidity, while the movements are abolished by the ultimate spastic state. The pattern of the movements has in most instances closely approximated to that described in Cases 1 and 2 reported above. The beginning of the jerk is more sudden than its subsidence, and in the patient of Martin, Macken, and Hess the resultant bizarre posture had scarcely dissolved before the next salvo began. The amplitude is usually increased by disturbance; in some cases there is a refractory period, during which the movement cannot be provoked by stimulation.

Secondly, choreiform, athetoid, or ballistic movements, transitory opisthotonus with or without torsion, conjugate ocular deviation, and grimacing, described in other cases, are probably variations of the complex movements already described. The elaborate semi-purposive gesture, as if the child were warding off a blow, repeated from time to time in Greenfield's third patient, is reminiscent of the attacks described so vividly in cases of subacute sclerosing leucoencephalitis.

Thirdly, there may occur a very rapid tremor of small amplitude—'movements so rapid that she appeared to tremble' (Dawson, 1934), 'shuddering movements affecting the whole body every half hour or so' (Greenfield, 1950, Case 2), or rhythmical tremor of a limb in a temporarily fixed posture (Greenfield, 1950, Case 3). In the later stages of the disease the patient of Martin, Macken, and Hess (1950) exhibited a fine tremor of the limbs after each involuntary spasm. 'Shivery' movements of the hands, as they were carefully folded upon the chest or brought up to the brow, were notable in our patients. A rapid generalized tremor, however, is a common enough finding in other conditions of decortication, for example those following anoxia. A feature which is worthy of comment in Case 1 was the decomposition of movements, and the remarkable speed and accuracy of the separate components of some voluntary movements.

The involuntary movements may not be conspicuous, and when slight are usually confined to the proximal segments of the limbs, as, for example, in a brief abduction by a few degrees at the shoulder or a slight flexion of the hip. Alternatively, in the later stages the only periodic movement may be a conjugate spasm of the eyes. Although involuntary movements have been prominent in the cases so far described, there is no reason why, in view of the diffuse nature of the disease, cases should not occur without them. They might, for example, be replaced by the inverse phenomenon, a periodic loss of tone difficult to detect in a child lying in bed. The peculiar phenomenon of 'echo' movements, seen in Case 1, has not been described before. We have observed the same phenomenon in a stuporous child suffering from an unknown type of subacute encephalopathy associated with increased protein in the cerebrospinal fluid; he had a hemiplegia,

and rhythmic jerking movements occurred in the hemiplegic side. His sister had died of an identical disease at the same age. The principal pathological lesion in this case, in which there were no inflammatory changes, was an unusual form of degeneration of the neurones and neighbouring axons in the lateral and medial nuclei of the thalamus, and complete destruction of the pyramidal cells of Sommer's sector. The important characteristics of this echo phenomenon are that (1) it occurs in stupor, (2) in both cases periodic involuntary movements were occurring, (3) the response to a painful stimulus is delayed, and is then superimposed upon the previous pattern of involuntary movement, (4) the response is a well-co-ordinated movement, or is a phrase such as 'I don't like that', and (5) it is repeated at intervals, gradually diminishing until only the pre-existing involuntary movement is discernible. In Case 1 periodic complexes were occurring in the electroencephalogram, but no periodic features could be made out in the tracings from the case of encephalopathy just mentioned. Finally, in both cases, although the nature of the disease was different, there was neuronal degeneration in the thalamus, in Sommer's sector of the hippocampus, and in the occipital cortex.

The increase in tone is of extrapyramidal distribution and character, but tends to be variable in the early and intermediate stages. The face, though it may be distorted by grimaces or chewing movements, is expressionless; but a full-blown Parkinsonian rigidity is exceptional. Frank pyramidal signs are found only in the late stage, and even in cases described in the literature as 'spastic' the plantar responses have been flexor until shortly before death. This paucity of pyramidal changes, and the predominance of involuntary movements of a periodic kind, are features which distinguish the disease clearly from Schilder's disease. A unilateral or bilateral grasp-reflex is common, but tonic neck reflexes do not occur. Incoordination of the limbs is common, but of variable degree; gait is disturbed by incoordination, by the posture of slight flexion of the knees with increased lumbar lordosis, and above all by akinetic attacks or the interpolation of involuntary movements. The posture in bed is generally one of adduction of the arms and flexion and pronation of the forearms, while the lower limbs are slightly flexed at hip and knee until the final stage, when they are spastic in extension.

Hemianopia is, like frank hemiplegia, uncommon, but cortical blindness is the rule in the last stage. In contrast with the intellectual impairment and extra-pyramidal features, involvement of the cranial nerves is slight. Papilloedema was present in the patient of Martin, Macken, and Hess (1950), and in Cases 2 and 3 reported here, while optic atrophy was observed in Case 3 of Brain, Greenfield, and Russell (1948), Cases 2 and 3 of Malamud, Haymaker, and Pinkerton (1950), and Greenfield's Case 3 (1950). Macular degeneration was observed in Case 3 of Malamud, Haymaker, and Pinkerton, and choroidoretinitis in Case 2 of Brain, Greenfield, and Russell. Pupillary abnormalities, ptosis, and ocular palsies are seldom evident and never early, and nystagmus is seen only in the late stage. Dysphagia, however, is common, persistent, and troublesome.

3. *The third stage.* The final stage is one of decortication, though not decere-

bration, with the posture already described: dementia is profound and vision absent, but the child may still start at a sudden noise. The amplitude of the involuntary movements diminishes, though their periodicity is maintained until hyperpyrexia and profuse sweating lead on to death.

In no case have general systemic signs of infection been present, and the impression is that the fever, which, though absent at the onset, appears in the middle stage and gradually increases, is of central origin. A polymorphonuclear leucocytosis of from 10,000 to 20,000 is the only change to be found in the blood. The one consistent change in the cerebrospinal fluid is the 'paretic' type of Lange curve, which has been present in all the cases in which it has been examined, and this change may occur in the first few weeks of the illness (see Case 4). This abnormality persists, although the reaction in the first tubes diminishes as the disease advances, as exemplified by Case 1 and by the case of Akelaitis and Zeldis (1942). The cell-content is normal, or but slightly increased, and the same applies to the protein-content of the fluid. Our knowledge of the distinctive clinical picture of this disease is based on a total of 15 cases and the four fatal cases reported in the present paper. We know from Case 5 that the condition may become arrested at an advanced stage, but it may well be that the disease can occur in a milder form, from which recovery is possible. If one may judge from the early symptoms in the fatal cases, such a mild form of the illness would consist of disorders of behaviour, deterioration of work at school, petit mal, akinetic attacks, perhaps myoclonic jerks, and choreiform movements. Although highly characteristic periodic complexes occurred in the electroencephalogram in the early course of the disease in Case 1, such complexes are usually not evident until the middle stage of the disease has been reached, and in mild cases no characteristic features might be seen; but some alteration of the colloidal-gold reaction in the cerebrospinal fluid is to be expected even in mild cases.

The Electroencephalogram

Changes in the electroencephalogram in subacute sclerosing leucoencephalitis and inclusion-body encephalitis have been described and discussed by Balthasar (1944), Radermecker (1949), Cobb and Hill (1950), Martin, Macken, and Hess (1950), and Clearkin and Millar (1952). In the early stages the alpha rhythm is present, but disturbed by diffuse 4- to 6-a-second activity, and by occasional high-voltage 3-a-second waves particularly in the frontal lobes. In addition, periodic, symmetrical complexes of a very characteristic kind occur. In the later stages all the normal frequencies are absent, and high-voltage slow waves occur in the areas of maximal cortical damage. In some cases slow spikes, positive, negative, or diphasic, interrupt the basal activity, and these are not accompanied by movements. Upon this background there occur periodic complexes, usually synchronous with the so-called myoclonic jerks. They consist most often of a diphasic wave-complex of 100 to 200 microvolts and a duration of 0.2 to 0.3 second, preceding a short succession of large waves of diminishing amplitude but increasing frequency, which are followed by a period of electrical inactivity,

or submerged in the basal slow activity. The pattern tends to be constant during a given recording, but varies slightly from day to day and from patient to patient. The initial diphasic wave appears to be the most important. In some cases such outbursts may be very rare; usually, however, they occur at intervals of six to 10 seconds. Sometimes they follow the involuntary movement, and the nature of the motor accompaniment may change while the form of the periodic outbursts remains constant. Furthermore, the electroencephalographic complexes continue during sleep, when the movements cease. Martin, Macken, and Hess (1950) noted that the complex can be provoked by a painful stimulus; in their patient the latent period of the provoked movement was often only 0.1 second, while that of the complex was of the order of one second. It is of interest that these authors stated that the level of consciousness was higher on the days when the periods were shorter. It was clear to them that the complexes are not the cause of the movement; neither are they the result of the arrival of proprioceptor impulses caused by the movement, for they continue in sleep. They concluded that the periodic movements and the electroencephalographic outbursts are two results of a single causal process; but their remarkable periodicity remains unexplained.

Pathology

The brain shows no gross alteration, though the cortex may be firmer than normal. Meningeal infiltration is minimal. Lesions in the cortex are widespread, with perivascular lymphocytic and plasma-cell infiltration, but without perivascular haemorrhages. There is a varying amount of neuronal degeneration, with at first central chromatolysis, and later loss of Nissl granules, shrinkage of the cytoplasm, and neuronophagia. In many of the affected neurones inclusion bodies may be seen. The appearance of these bodies has been described and illustrated by Brain, Greenfield, and Russell (1948). The intranuclear inclusions vary in size from 3 to 10 μ ; when small they lie centrally, displacing the nucleolus, and separated by a clear zone from the nuclear membrane, on which the chromatin is condensed; when large they fill the nucleus completely, only a few fragments of chromatin being seen on their surface. With haematoxylin and eosin they vary in colour from rose to mauve; Mallory's phosphotungstic-acid-haematoxylin stains them purple in contrast to the pink-staining nucleolus. With Lendrum's phloxin-tartrazine the smaller inclusions stain bright red, the larger ones orange. Inclusion bodies may occasionally be found in the nuclei of swollen oligodendroglial cells. The cytoplasmic inclusions are more eosinophilic than the intranuclear. In the early stages they may be multiple and granular, but as the cell degenerates they coalesce to form single lobulated hyaline masses. The inclusions in this disease are regarded as quite distinct from those seen in cases of encephalitis due to herpes simplex virus (in which the course is more acute, and there is degeneration of the walls of blood-vessels, with fibrinous exudate and polymorphonuclear infiltration) in that they are hyaline, and both intranuclear and intracytoplasmic, whereas the inclusions of herpes simplex are granular, and often have fine radiating lines connecting them to the nuclear

membrane. Together with the neuronal disease of subacute inclusion-body encephalitis there is usually marked microglial hyperplasia and astrocytic gliosis, often with hyperplastic and paired astrocytes. On the whole the occipital and temporal cortex has been more severely involved than the frontal and hippocampal, though in the latter there is particular involvement of Sommer's sector. The cerebellum is spared, and the cord rarely affected. The basal ganglia show similar subacute changes, but the thalamus is more heavily involved, though here nuclear changes are less definite. In general, involvement of the caudate and lenticular nuclei has been slight, an interesting feature in view of the predominance of extrapyramidal signs. Similarly the nuclear masses of the midbrain have shown only moderate changes, but affection of the pontine nuclei, with typical inclusion bodies, perivascular cuffing, and the formation of glial stars, has been prominent. In the cerebellum there may be some loss of Purkinje cells. Inclusion bodies have not been seen in the dentate nuclei, though they have been reported in the inferior olives.

Whereas Brain, Greenfield, and Russell (1948) remarked of their cases that there was 'no more alteration of the white matter than would be accounted for by destruction of cortical neurones or spread of inflammation into subcortical zones', significant changes in the white matter were observed in the cases of Malamud, Haymaker, and Pinkerton (1950); in these there were intranuclear, but not intracytoplasmic inclusions, a greater degree of degeneration of the white matter with dense gliosis, and in one chronic case neurofibrillary changes of the Alzheimer type. Furthermore, in Case 3 of Brain, Greenfield, and Russell there was diffuse greyish-white discolouration of the white matter in many areas, some friable softenings, and areas in which there was loss of axis cylinders and gliosis. Together with the three cases of Malamud, Haymaker, and Pinkerton, that of Martin, Macken, and Hess (1950) effectively bridges the gap between inclusion encephalitis and subacute sclerosing leucoencephalitis. This fully documented case, which displayed periodic involuntary jerks and dystonic movements, and disturbances of gait similar to those described previously in cases of subacute sclerosing leucoencephalitis, had pathological features common to both conditions. Both grey and white matter were involved, the disease affecting predominantly the occipital poles, in a diffuse subacute inflammation with lymphocytic and plasma-cell perivascular cuffing. In the grey matter there were irregular ischaemic zones and areas of necrosis, showing a marked glial reaction with numerous rod cells and swollen astrocytes, these changes being particularly marked in layers V and VI. The white matter of the hemispheres was diffusely affected, though there was a predilection for the subcortical white matter. Areas of necrosis occurred in the occipital white matter. Numerous fat-granule cells were present, especially round the vessels. There was dense glial proliferation, with the formation of glial nodules. Neuronal damage was fairly conspicuous in the globus pallidus and thalamus, but not evident in the putamen. Sommer's sector was heavily affected. The subthalamic nucleus, red nucleus, and field of Forel were not involved, but the ventrolateral group of the pontine nuclei and the inferior olives showed moderately severe changes. There

was slight involvement of the cerebellar white matter, but none of the cortex or the dentate nucleus. Martin, Macken, and Hess classed this case as one of subacute sclerosing leucoencephalitis, summarizing the histological features of the latter as (1) moderate fibroglial infiltration of the white matter, (2) a variable degree of demyelination, (3) diffuse lymphocytic and plasma-cell infiltration, (4) predominant affection of the white matter, but with some spread into the overlying cortex, and (5) relatively minor changes in the subcortical grey matter and cerebellum. Their case, however, showed in addition areas of necrosis, sometimes going on to cavitation, in both white and grey matter. Greenfield was able to demonstrate inclusion bodies in this case, and they were found also in material from the second case of Dubois, van Bogaert, and Lhermitte (1949), originally described as an example of subacute sclerosing leucoencephalitis.

It thus appears that, although there have been differences in the distribution of lesions between grey and white matter in cases of inclusion encephalitis reported in England and the United States, it is improbable that a fundamental distinction can be maintained between the two conditions. Greenfield (1950) remarked upon the clinical similarity between all the cases reported under the two names, and van Bogaert (1952) accepted their identity, though preferring the term subacute sclerosing leucoencephalitis because it emphasizes the important changes in the white matter. The name 'subacute sclerosing panencephalitis' suggested by Greenfield (1950) has much to commend it. Subacute sclerosing leucoencephalitis as described by continental writers is, like inclusion encephalitis, limited to the first two decades, and begins with intellectual impairment and an indifference which contrasts strongly with the disorderly conduct encountered in most other dementias of childhood, though there may be episodes, mainly nocturnal, of psychomotor activity and hallucination. Occasionally the onset may be more rapid, with fever, headache, and delirium. Van Bogaert originally regarded dysphasia and apraxia as significant early features, though it is difficult to evaluate their importance in the face of a progressive dementia. The main features of the disease have been admirably summarized by Lhermitte (1950) and Macken and Lhermitte (1950), and its mode of evolution bears a close resemblance to the three stages of inclusion encephalitis already outlined. The only outstanding clinical difference appears to be that in the cases reported on the Continent the involuntary movements have been more florid and complex.

Aetiology

Although the presence of intranuclear and intracytoplasmic inclusions is strong presumptive evidence that a virus is responsible for the disease, no virus has yet been isolated; the inclusion bodies are certainly not regarded as degenerative. The involvement, in inclusion encephalitis, of neurones in the cortex and brain-stem is, however, topographically similar to that seen in varieties of encephalitis known to be due to a virus, while the involvement of white matter in this diffuse and chronic inflammation can no longer be regarded as an argument against a viral cause. Histopathologically, of course, the condition remains

quite distinct from the primarily demyelinating diseases. Lhermitte (1950) and Macken and Lhermitte (1950), while emphasizing the pathological singularity of subacute sclerosing leucoencephalitis, which they regarded as allied to inclusion encephalitis, drew attention to the many points of resemblance between this apparently new disease and certain atypical examples of Type B encephalitis, St. Louis encephalitis, and Russian encephalitis on the one hand, and the sporadic panencephalitis nodosa of Pette and Döring (1939) on the other. Lhermitte suggested that many of the histological peculiarities of subacute sclerosing leucoencephalitis might be due merely to its occurrence in childhood. Animal inoculation has not yet provided proof that inclusion encephalitis and subacute sclerosing leucoencephalitis are due to virus infection, though in one of the cases of Macken and Lhermitte (1950) a neurotropic virus was transmitted successively to two rabbits, while in the case of Martin, Macken, and Hess (1950) a virus was transmitted by inoculation of cerebrospinal fluid through four passages in white mice, and by inoculation of brain-tissue through two passages. The virus was not identified serologically. Animal inoculation was unsuccessful in Dawson's two cases (1933, 1934) and in Cases 2 and 3 of Brain, Greenfield, and Russell (1948). Animal inoculation was carried out in our Cases 1, 2, 3, and 4 without success. From concentrates of the brain in Case 1 a virus was isolated from mice and, though its initial behaviour was not typical, it was ultimately proved to be the virus of herpes simplex; but there is conclusive evidence that it was not the cause of the disease.

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Summary

Five cases of subacute inclusion encephalitis occurring in this country are reported. Four of these were fatal, while in the fifth case the disease appears to be arrested in its fourth year. Clinically, electroencephalographically, and pathologically the fatal cases bear a very close resemblance to instances of subacute sclerosing leucoencephalitis, and the relationship between these forms of progressive panencephalitis occurring in children is discussed.

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Fig. 9. Case 1. Horizontal section of the left occipital lobe, showing extensive demyelination (Loyez stain)

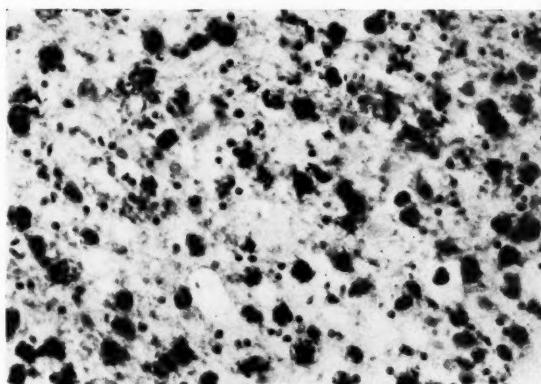


Fig. 10. Case 1. Section of occipital white matter, showing complete breakdown of myelin into fat-granule cells (Scharlach-R-haemalum)

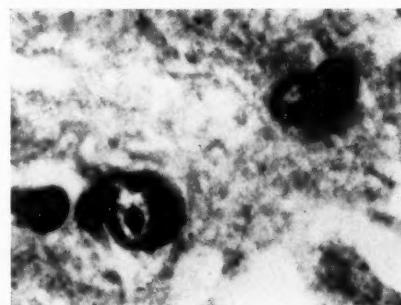


Fig. 11. Case 1. Occipital cortex. A nerve-cell is seen with a small intranuclear inclusion and larger flocculent cytoplasmic inclusions. The small dark nucleolus lies against the nuclear membrane. A pair of recently divided astrocyte nuclei, with swollen cytoplasm, is also seen (Lendrum's phloxin tartrazine stain, $\times 1,000$)

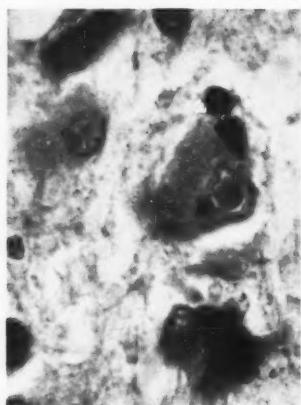


FIG. 12 a.

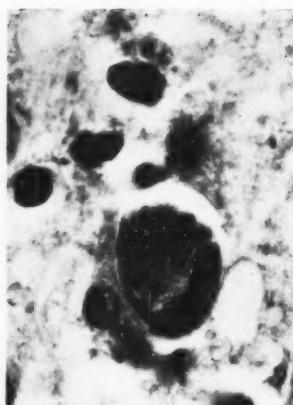


FIG. 12 b.

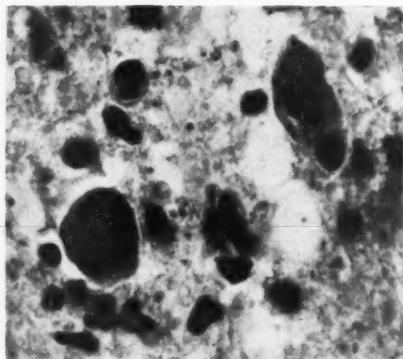


FIG. 12 c.

Figs. 12a, 12b, and 12c. Case 1. Nuclei pontis, showing nerve-cells with intranuclear inclusion bodies. The nucleus is eccentric, and the nucleolus is pushed to one pole of the nucleus (Lendrum's phloxin tartrazine method. Figs. 12a and 12b $\times 1,000$; Fig. 12c $\times 750$)

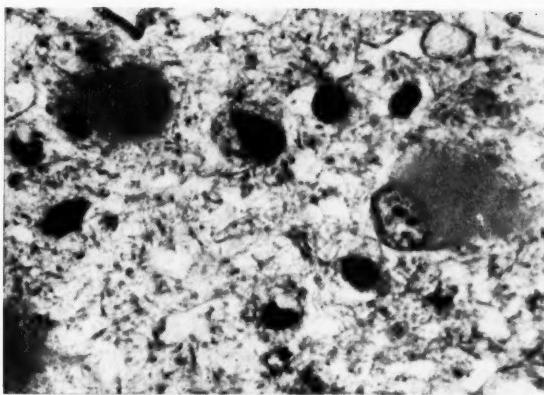


Fig. 13. Case 1. Section of occipital white matter, showing swollen astrocytes and fibrous gliosis (phosphotungstic-acid-haematoxylin, $\times 1,000$)

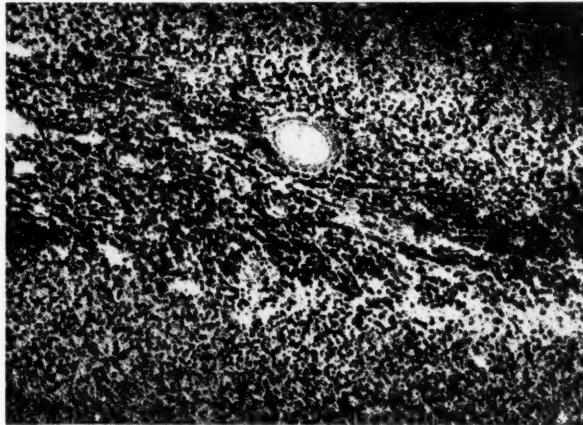


Fig. 14. Case 2. Section of occipital white matter through optic radiations, showing local breakdown of myelin and formation of fat-granule cells (Scharlach-R-haemalum)

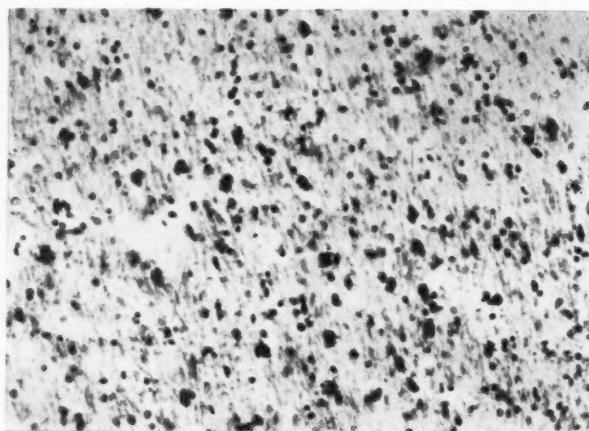


Fig. 15. Case 3. Section of occipital white matter showing partial demyelination and formation of fat-granule cells
(Scharlach-R-haemalum)

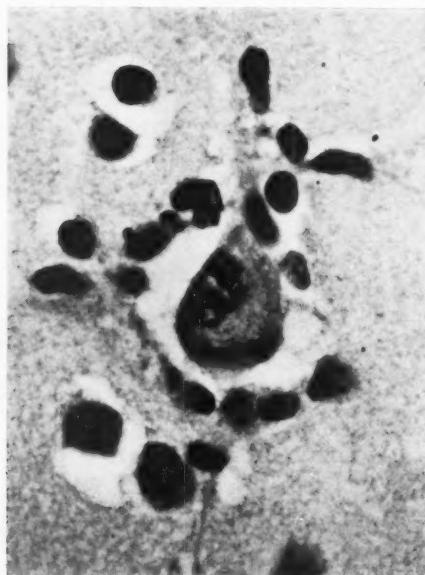


Fig. 16. Case 4. A pyramidal cell from the third layer of the cerebral cortex, showing satellitosis. The nucleus is eccentric and contains a small acidophilic inclusion in addition to the nucleolus; this inclusion body lies towards the base of the cell. Near the margin of the cytoplasm at the base of the cell are two flocculent acidophilic inclusions,
(haematoxylin and eosin, $\times 1,000$)

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HYPERTENSION IN CARDIOVASCULAR BERI-BERI¹

By J. H. WALTERS

(From the State Hospital, Kuwait, Arabia)

THE manifestations of aneurin deficiency in any group of patients tend to follow a definite pattern and time-relationship, but often show extreme variation between different groups. The particular form which they take is determined not only by the acuteness of the deficiency, but also by the degree of physical exertion which is demanded of the subject under these conditions of deficiency. Severe exertion, maintained on a diet adequate in total calories but deficient in aneurin relative to the demands of carbohydrate metabolism, will lead to changes in the cardiovascular system, whereas relative starvation, by limiting activity, tends to protect this system and allows the neurological manifestations of beri-beri to dominate the clinical picture, usually after a longer interval than that required for the appearance of cardiovascular disease. By a daily analysis of the diet issued to captives held by the Japanese during the recent war, Smith and Woodruff (1951) have shown that the critical value for the aneurin/non-fat-calorie ratio, below which beri-beri will appear, is 0·4 mg./1,000 non-fat calories. Many examples can be quoted of a specific type of reaction among groups of persons exposed to aneurin deficiency, yet the factors which determine the actual pattern of the manifestations are little understood. Thus, among prisoners of war held by the Japanese in Singapore, de Wardener and Lennox (1947) reported that an outbreak of encephalopathy of the Wernicke type heralded the onset of deficiency diseases, and appeared after only six weeks of captivity. In civilian internment camps in Hong Kong and Singapore, however, the earliest manifestation of deficiency disease was cardiovascular beri-beri, which was noted by Smith and Woodruff (1951) to have begun in a sharp outbreak 87 days after the fall of these cities. Polyneuritis, on the other hand, developed at a later date. An outbreak of beri-beri almost exclusively affecting the cardiovascular system occurred in West African troops in Mauritius, and was investigated by Cullinan, Kekwick, Watts, and Titman (1946). Their 22 cases of dropsy all conformed closely to a single pattern, in which evidence of peripheral neuritis was slight and signs of intrinsic cardiac damage were uncommon, the oedema being apparently due to changes in the peripheral blood-vessels.

From time to time attention has been drawn to the unexpected occurrence of arterial hypertension among series of patients who undoubtedly had cardiovascular beri-beri, though as yet no investigation of the underlying mechanism appears to have been made. For instance, Wenckebach (1934) stated that 'The arterial pressure, at least the systolic pressure, is also maintained for a long time, and one is astonished to find pressures over 150 mm. in severe cases'.

¹ Received August 13, 1952.

Casanova (1946), reporting a widespread outbreak of cardiovascular beri-beri in black Senegalese troops in North Africa, noted that the blood-pressure was raised in proportion to the pulse-rate, while Cruickshank (1946) reported arterial pressures in excess of 130/90 mm. Hg in 51 out of 189 patients who were suffering from the 'painful feet syndrome', with evidence of an associated aneurin deficiency, during captivity in Japanese hands in Singapore. Occasional examples have also been reported by Weiss and Wilkins (1937), by Mitchell and Black (1946), by Gelfand and Bellet (1949), and by Walters and Smith (1952). Of particular interest was the observation by Weiss and Wilkins (1937) of a case of cardiovascular beri-beri in which transient arterial hypertension followed treatment with aneurin. The same association was also evident in three middle-aged men in the series of recently released prisoners of war treated in Singapore by Mitchell and Black (1946). In these three patients signs of left ventricular cardiac failure, precipitated by hyperpiesis (the maximum blood-pressure recorded was 220/110 mm. Hg) developed after they had received large daily doses of aneurin for two weeks. Complete recovery, with reversion to a normal blood-pressure, ensued after 10 to 17 days.

The present paper concerns an outbreak of acute cardiovascular beri-beri among men engaged in the pearl-fishing fleet in the Persian Gulf in the summer of 1951. Eleven severe cases came under medical observation, of which eight form the subject of this report; the records of the remaining three patients, who were treated in a different hospital, have been examined by the courtesy of Dr. B. Y. Voss, of the American Mission Hospital, Kuwait. All these cases conformed to a single clinical picture, and all began to show symptoms within a few weeks of one another, about three months after the fleet had put to sea. The features of their disease were (1) gross anasarca, (2) myocardial damage, (3) arterial hypertension, and (4) absence of signs, or minimal signs, of peripheral neuritis. A final case, more recently observed, has been added, in which the disease arose under similar circumstances and the response to aneurin was typical of that seen in the other cases in the series. The diagnosis was based on (1) the circumstances under which the outbreak developed, (2) the normal serum-protein levels, (3) the absence of gross renal disease, (4) the occurrence of tenderness of the calf-muscles in most cases, and (5) the good response to treatment with aneurin in four of the nine similar cases. Justification of the report on so small a series rests on the association of hypertension with cardiovascular beri-beri, which was shown in every case at some phase of the disease. The report concerns a problem of which the explanation is still obscure. Since the clinical features shown by these men were undoubtedly related to the peculiar circumstances in which the disease developed, a short description of the pearl-fishers' life at sea must be given.

Pearl Diving

Pearl diving is a seasonal occupation: the fleet sets out at midsummer and remains on the oyster-beds until mid-October. Although launches visit the ships during this period with supplies, and merchants go out to buy the pearls,

the crews do not come ashore. The ships, called 'booms', are wooden sailing-vessels of about 100 tons gross weight, with open decks on which the crews live under awnings. While in action, every man except the captain works either as a diver or as a diver's mate. The divers use no apparatus other than a wooden nose-clip. They descend rapidly to the sea-bed on a rope weighted with a large stone, which is then drawn up. They remain under water for 60 to 90 seconds, and then either swim up or are rapidly drawn to the surface by a light rope carrying a loop into which the foot is placed. The depth of the dive is from 12 to 30 feet, and each diver may make 50 or more descents every day. Their diet consists of polished rice, fresh fish, and dates, either fresh or dried; the rice and fish are cooked in oil with condiments. The men who dive eat only a few dates during the working day, but consume a big meal of rice in the evening. The rest of the crew take two meals a day. It is well known that the divers tend to lose weight during the fishing season, yet permanent impairment of health has previously been rare, and the town of Kuwait contains many active elderly men who have dived for pearls regularly for many years. The causes of the outbreak of beri-beri in the pearl-fleet on the present occasion will be discussed later.

The first two patients were admitted to the State Hospital, Kuwait, in mid-September 1951, and the remaining six during the succeeding four weeks. Six of them were divers, and the other two worked in the ships as divers' mates. The first two patients were noticed to be hypertensive on admission, but no causal relationship between the arterial hypertension and beri-beri was suspected until the third patient (Case 3) also began to show a rising blood-pressure during treatment. A more detailed series of observations were then initiated, and these showed the phenomenon to be common among the patients.

Case Reports

Case 1. Hassan bin Mohammed, aged 50 years. This Kuwaiti pearl-diver had been at sea for about 10 weeks when he began to suffer from severe headaches, and his legs and trunk began to swell. On admission to hospital two weeks later he showed considerable oedema of the legs, genitalia, and lumbar region. The calf-muscles were tender on pressure, but the tendon-reflexes were active. His haemoglobin concentration was 8.4 gm. per 100 ml.; his urine contained traces of albumin and scanty red blood-corpuscles. He was hypertensive on admission (blood-pressure 174/94), and six days later developed an acute hypertensive crisis with severe headache, restlessness, and disorientation, necessitating intravenous morphine for the control of his symptoms. On the following day his blood-urea was found to be 28 mg. per 100 ml.

After two weeks' treatment with iron and aneurin (150 mg. daily by mouth) all his oedema had cleared, and his haemoglobin concentration had risen to 11.4 gm. per 100 ml., but renal function remained slightly impaired, with a maximum concentration of urea in the urine of only 1.8 gm. per 100 ml. two hours after a test dose of 50 gm. Fig. 1 shows the fluctuation in his blood-pressure. This first case was considered to be an example of 'wet beri-beri' superimposed on essential hypertension, without evidence of myocardial deficiency, although slight enlargement of the left ventricle was seen in the X-ray.

Case 2. Ismail Juma, aged 25 years. This man was a very muscular Negro from Dubai, who was not himself a diver but remained in the ship attending to the divers. He also had been at sea for 10 weeks when, about two weeks before admission, his legs and then his whole body began to swell. On examination he

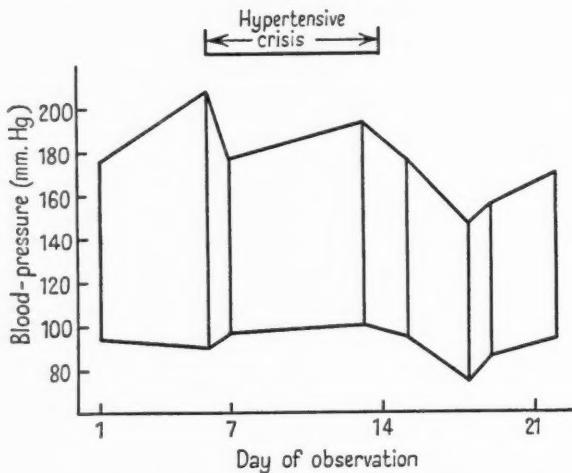


FIG. 1. Case 1. Hassan bin Mohammed. Blood-pressure.

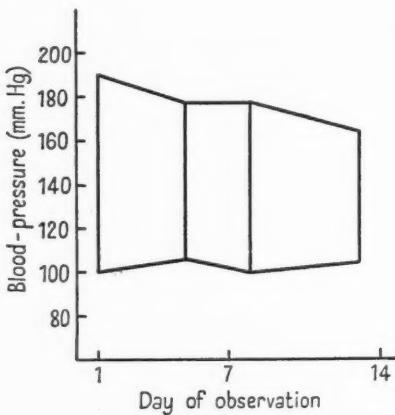


FIG. 2. Case 2. Ismail Juma.
Blood-pressure.

showed gross oedema of the whole body up to the level of the clavicles; there was, however, no evidence of cardiac enlargement or embarrassment. The blood-pressure was 190/100, but declined subsequently (Fig. 2). The urine contained traces of albumin and scanty red cells, but no casts. All oedema cleared after seven days' treatment with aneurin, 150 mg. daily by mouth.

Case 3. Juma Hassan Abaid, aged 30 years. This powerfully built man from Muscat, after working as a diver for nearly four months, was compelled to give

up owing to constant pain in the epigastrium followed by swelling of the legs and body. At the same time his gums became swollen and his teeth became loose. On admission he showed both extreme anasarca and signs of scurvy. The mouth showed typical severe scorbutic lesions, and there was a haemorrhage

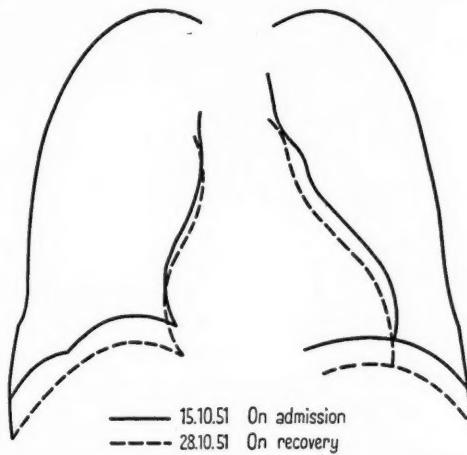


FIG. 3. Case 3. Juma Hassan Abaid. Orthodiagram of chest.

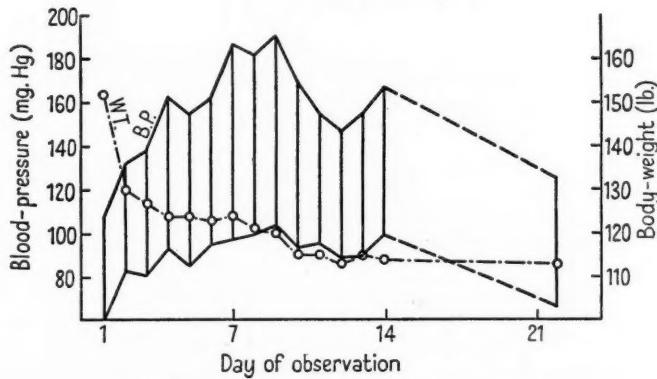


FIG. 4. Case 3. Blood-pressure and body-weight.

into the subcutaneous tissues of the dorsum of the left hand. The skin showed follicular hyperkeratosis with some perifollicular haemorrhages. The limbs, face, and whole trunk were swollen, and considerable ascites was also present. Although the calf-muscles were tender on pressure, the tendon-reflexes were retained. There was radiological evidence of cardiac enlargement, which had become significantly less two weeks later after treatment with aneurin (Fig. 3). The haemoglobin concentration, initially 6.7 gm. per 100 ml., rose to 10.5 gm. per 100 ml. after three weeks' treatment. The blood-urea was 25 mg. per 100 ml. There was no clinical evidence of myocardial damage, and the electrocardiogram only showed slight left axis deviation. There was an impressive response to aneurin therapy, which comprised an initial intravenous injection of 50 mg.,

followed by intramuscular injections of 25 mg. for the next two days, after which he received a daily oral dose of 30 mg. throughout the next 10 days. His weight showed a loss of 22 lb. after 24 hours, and a total loss of 39 lb. in 12 days. The blood-pressure, which was low on admission, showed a sustained rise during

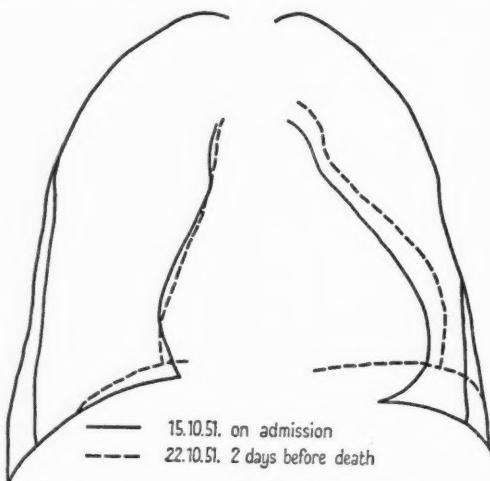


FIG. 5. Case 4. Khamis bin Rubia.
Orthodiagram of chest.

the period of treatment, and this hypertensive phase was accompanied by severe headache. The scorbutic lesions cleared up rapidly on treatment with a daily dose of 400 mg. of ascorbic acid. The blood-pressure fluctuations and changes in weight are recorded in Fig. 4.

Case 4. Khamis bin Rubia, aged 25 years. This man was a well-developed young Negro, who had been at sea for four months in the same ship as Juma Hassan Abaid, and had also been working as a diver. Epigastric pain and swelling of the legs heralded the onset of his illness, after he had been at sea for three months. On admission he showed tense oedema of the whole body, including the face, on which swelling of the lower eyelids was prominent. Moderate orthopnoea was recorded. The apex beat was felt in the fifth left interspace $4\frac{1}{2}$ inches to the left of the mid-sternal line, and this moderate degree of enlargement was confirmed by X-ray (Fig. 5). Small bilateral pleural effusions were present, the liver was palpable in the epigastrium and was somewhat tender, and free fluid was evident in the peritoneal cavity. Nevertheless the pulse-rate was only 92 per minute, the pulse was regular, the apical first sound was good and pure, and the heart did not seem to be severely embarrassed. The electrocardiogram (Fig. 6a) showed low-voltage deflections, flat T waves in leads I, II, and III, and an inverted T wave in lead CR₁. Investigation showed slight albuminuria with scanty erythrocytes and granular casts, a haemoglobin concentration of 10.4 gm. per 100 ml., and a serum-protein concentration of 7.7 gm. per 100 ml. (albumin 3.8 gm., globulin 3.9 gm.). The Kahn reaction was positive in the serum.

Treatment comprised iron by the mouth and aneurin, of which he received 50 mg. intravenously on admission, 25 mg. subcutaneously on each of the next two days, and 30 mg. a day by mouth thereafter. During the next eight days,

although his pulse-rate fell steadily to 64 per minute, his weight hardly diminished and his blood-pressure steadily rose. These findings are recorded in Fig. 7. On the ninth day he developed fever and a cough, and râles were heard over the right lower lobe; it was evident that bronchopneumonia had supervened. An

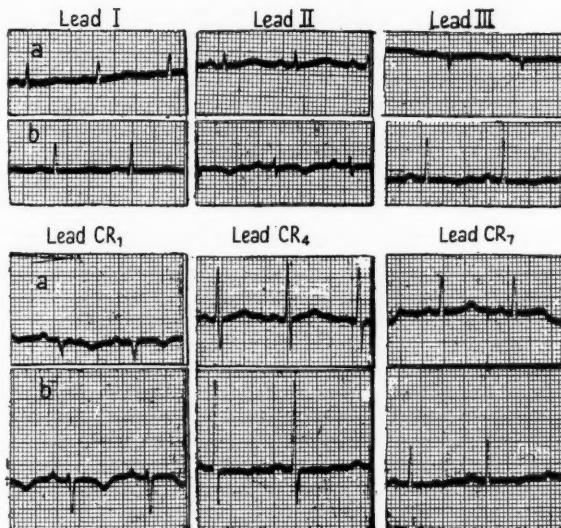


FIG. 6. Case 4. Electrocardiograms (a) on admission, (b) after eight days' treatment, one day before death.

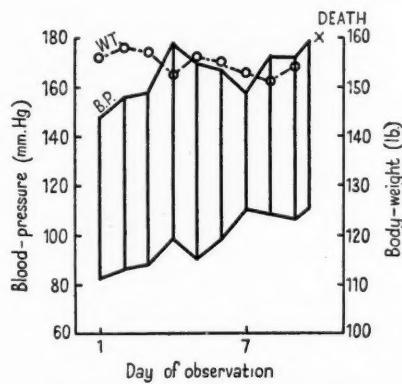


FIG. 7. Case 4. Blood-pressure and body-weight.

X-ray showed further enlargement of the heart, marked congestion of the right lung, and increased pleural effusions (Fig. 5). He rapidly became very restless and distressed, and examination now showed a well-marked gallop rhythm at the apex. An electrocardiogram taken at this time showed slightly increased amplitude of the deflections, but T_2 and T_3 had now become inverted (Fig. 6b). He

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was nursed in an oxygen tent, morphine and atropine, with mersalyl 2 ml., were injected, and 350 ml. of blood were removed by venesection. In spite of these measures he died of acute pulmonary oedema on the following morning. This patient showed no favourable response to aneurin during eight days, and died of

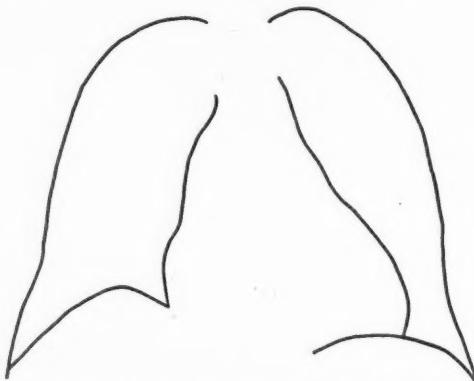


FIG. 8. Case 5. Aäid bin Khadim. Orthodiagram of chest on admission, one day before death.

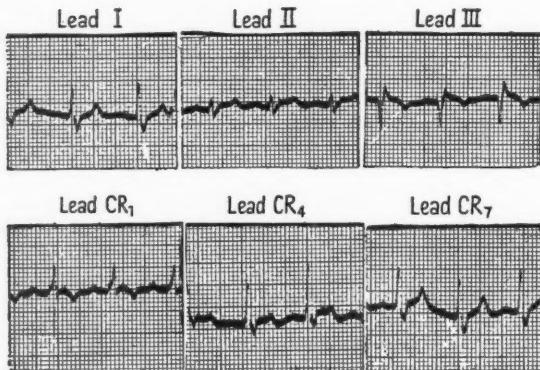


FIG. 9. Case 5. Electrocardiogram on admission, one day before death.

cardiac failure provoked by arterial hypertension and precipitated by an acute respiratory infection.

Case 5. Aäid bin Khadim, aged 30 years. This man, a muscular young Negro, was admitted at the same time as his shipmates (Cases 3 and 4). He also had been diving for four months, but had only become ill about 10 days previously. He presented a clinical picture similar to that of Case 4, with tense oedema of the whole body up to the clavicles, but in his case orthopnoea was much more severe. In addition he showed signs of scurvy—a haemorrhage into the subcutaneous tissues of the right hand, and extensive follicular keratosis of the skin. The cardiac boundaries were indefinite, and the apex beat was weak but regular at a rate of 100 per minute, with a tic-tac rhythm. The blood-pressure

was low, 96/48 mm. Hg, with 6 mm. alternation. The cervical veins were engorged, the liver was tender and palpable to four fingers' breadth below the costal margin, and moderate ascites was found. He was given an intravenous injection of 50 mg. of aneurin on admission in the evening, and a further 50 mg.

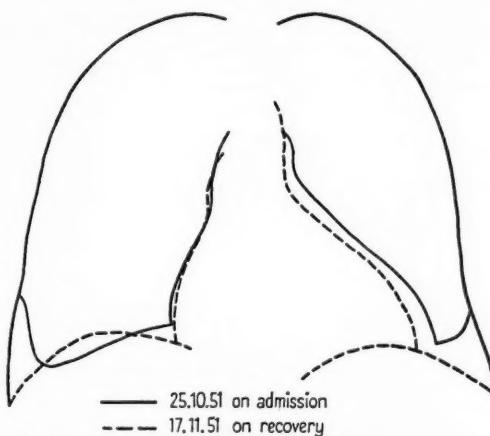


FIG. 10. Case 6. Ibdah bin Dhahi. Orthodiagram of chest.

were injected into the muscles six hours later. At midnight he seemed somewhat relieved, and his pulse-rate had fallen to 90 per minute; but early the following morning he died in acute pulmonary oedema. A small section of the wall of the left ventricle was removed through an intercostal incision immediately after death. This showed the myocardial fibres to be separated by acidophilic oedema fluid; their pattern was blurred, and their striation indistinct. Hydropic degeneration of the fibres themselves could not be detected. An X-ray taken on admission (Fig. 8) showed an enlarged heart with a prominent conus arteriosus, and an electrocardiogram indicated grave myocardial damage (Fig. 9).

Case 6. Ibdah bin Dhahi, aged 36 years. This man, an Arab from Kuwait, had been working at sea in the pearl-fleet as a diver's mate for four months. Eight days before admission he began to experience epigastric pain, and five days later his legs began to swell.

He was a sturdy, muscular, middle-aged man, who showed firm oedema of the limbs and trunk up to the level of the nipples, together with some swelling of the eyelids. The heart showed tachycardia with a regular rhythm, the resting rate being 112 per minute. The apical first sound was short and poor—a tic-tac rhythm—but there were no bruits. The blood-pressure on admission was 138/70. There was radiological evidence of moderate cardiac enlargement, with small bilateral pleural effusions (Fig. 10). The calf-muscles were tender on compression, but there were no objective sensory changes, and the tendon-reflexes were active. Investigation showed a haemoglobin concentration of 9.8 gm. per 100 ml., traces of albumin and a few granular casts in the urine, and blood-urea 60 mg. per 100 ml. The serum-protein concentration was 5.4 gm. per 100 ml. (albumin 3.26 gm., globulin 2.14 gm.). The Kahn reaction was positive in the serum. An electrocardiogram showed sinus tachycardia, with inversion of the T

wave and an elevated ST segment in lead III (Fig. 11*a*). Aneurin was given in heavy doses by both oral and parenteral routes (150 mg. daily by mouth, and intramuscular injections of 100 mg. daily for five days, then 25 mg. for a further five days). His condition showed no improvement during this period; there was

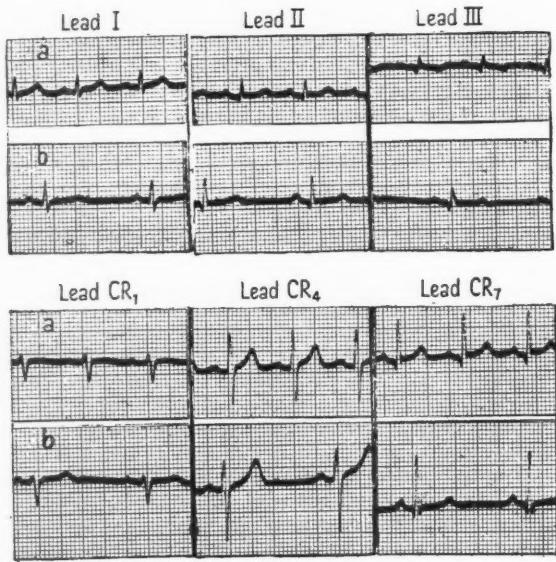


FIG. 11. Case 6. Electrocardiograms (*a*) on admission, (*b*) after three weeks' treatment.

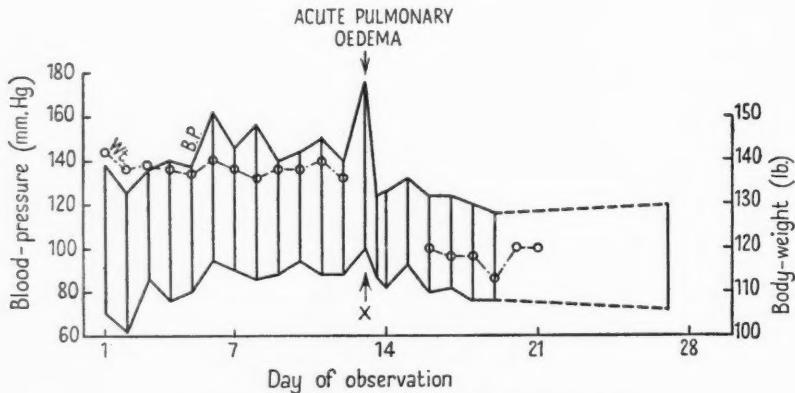


FIG. 12. Case 6. Blood-pressure and body-weight.

no diuresis, his weight remained constant, and his blood-pressure rose steadily (Fig. 12). This phase of progressive arterial hypertension culminated on the 13th day in an attack of acute pulmonary oedema. His condition remained critical throughout the next 24 hours, during which he was nursed in an oxygen tent, a venesection was performed, and morphine and mersalyl were injected,

together with 100 mg. of pentamethonium bromide, every four hours. Blood drawn at this time showed a serum-protein concentration of 6.48 gm. per 100 ml., an albumin/globulin ratio of 2.5 to 1, and a blood-urea concentration of 62 mg. per 100 ml. The measures outlined above were followed by steady im-

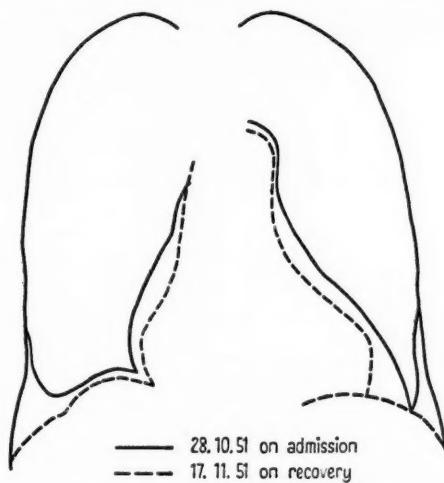


FIG. 13. Case 7. Ahmad bin Salim.
Orthodiagram of chest.

provement; the blood-pressure fell to its initial level, and all oedema disappeared. The electrocardiogram taken on his discharge, however, still showed low-voltage deflections, though T was now upright in leads III and CR₁, and the elevated ST segment in lead CR₄ was no longer present (Fig. 11b). The course of events in this patient, after treatment with heavy doses of aneurin, followed very closely that seen in Case 5, but in this case a fatal outcome was narrowly averted by measures taken to lower the arterial tension.

Case 7. Ahmad bin Salim, aged 40 years. This man, a big, powerfully built Arab from Kuwait, had been diving for three and a half months when he fell ill. Eight days before admission his legs began to swell, and thereafter the oedema rapidly increased until, on admission, it extended up to the level of the second rib and also involved the face. The heart was moderately enlarged (Fig. 13); the beat was regular at a resting rate of 92 per minute. A typical gallop rhythm was heard at the apex. The blood-pressure was 168/80, with 8 mm. of alternation. Small bilateral pleural effusions were present (Fig. 13), and ascites was found, though the liver was not palpably enlarged. There was no evidence of peripheral neuritis. An electrocardiogram showed sinus tachycardia, low-voltage deflections, and occasional ventricular extra-systoles (Fig. 14a). Examination of the blood showed a haemoglobin concentration of 12.3 gm. per 100 ml., serum-protein 6.1 gm. per 100 ml. (albumin 3.8 gm., globulin 2.3 gm.), and a negative Kahn reaction. The urine was normal. On treatment with aneurin (100 mg. by intramuscular injection and 150 mg. by mouth, daily for seven days) his weight fell steadily, but his blood-pressure rose (Fig. 15). Although all signs of oedema had cleared by the eighth day, his weight did not become constant until the 12th day. At the end of the third week of treatment the cardiovascular system was clinically normal, and improvement was

seen in the electrocardiogram, which now showed deflections of increased amplitude and improvement in the form of the T waves (Fig. 14*b*). In spite of the good

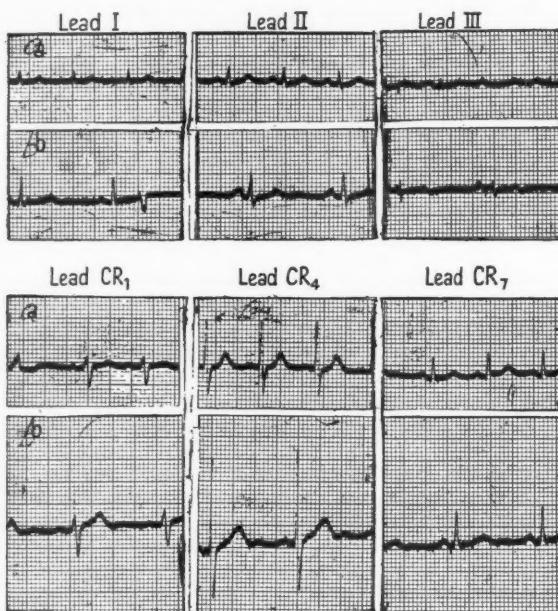


FIG. 14. Case 7. Electrocardiograms (a) on admission, (b) after three weeks' treatment.

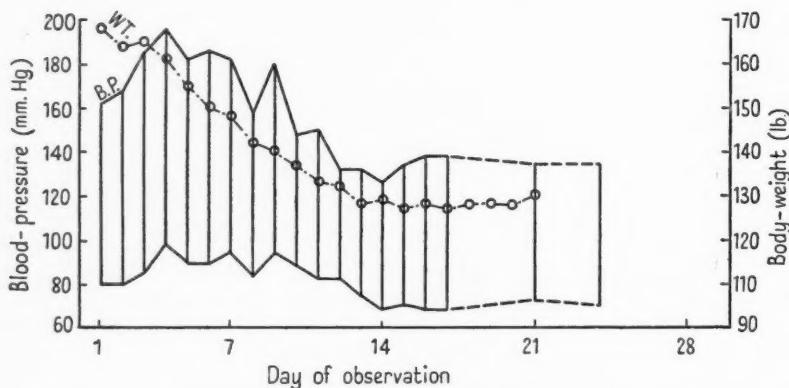


FIG. 15. Case 7. Blood-pressure and body-weight.

clinical response to aneurin this patient, too, exhibited the early increase in arterial pressure which was characteristic of the series.

Case 8. Ilmas bin Awlad, aged 35 years. This man was a tall, lightly built Negro, who had been at sea as a pearl-diver in the same ship as the patients

numbered 3, 4, and 5. He had been suffering for 15 days from increasing breathlessness with swelling of the limbs and trunk; his condition on admission to hospital was one of grave pulmonary oedema. He was extremely restless, with severe orthopnoea and almost continuous cough. The limbs were tensely

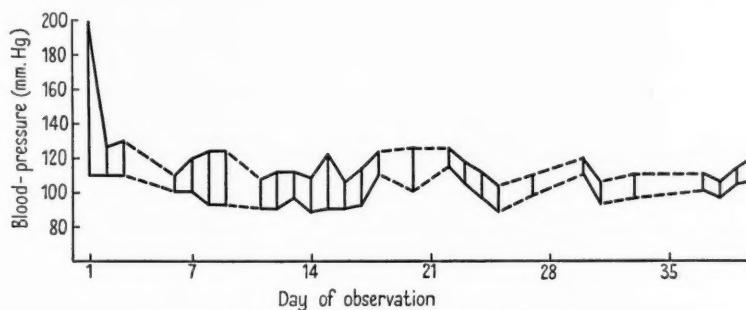


FIG. 16. Case 8. Ilmas bin Awlad. Blood-pressure.

swollen, and there was firm oedema of the body up to the level of the xiphisternum. The veins of the neck were engorged, and the liver was palpably enlarged to two fingers' breadth below the costal margin. The respiration-rate was 60 per minute, and the pulse-rate 120; the blood-pressure was 198/110. A loud gallop rhythm was heard at the apex. The patient was placed immediately in an oxygen tent, in which he was nursed for the next five days. Morphine and atropine were injected and a venesection was done, after which he was given aneurin 100 mg. and mersalyl 2 ml. by the intravenous route. An examination of the blood gave the following results: haemoglobin 10.4 gm. per 100 ml.; serum-protein 6.48 gm. per 100 ml. (albumin 3.8 gm., globulin 2.68 gm.); urea 44.5 mg. per 100 ml.; Kahn reaction negative. The urine was of low specific gravity, and contained a trace of albumin and scanty granular casts. In spite of a second intravenous injection of aneurin 100 mg., and daily intramuscular injections of 50 mg. thereafter, he remained in a condition of severe cardiac decompensation throughout the first five days of his treatment, while there was little diminution in his oedema, although an injection of mersalyl 2 ml. was repeated daily.

The gallop rhythm persisted during the first two weeks of treatment, and even on his discharge six weeks after admission the apical first sound was short, soft, and of poor quality. The diastolic pressure remained constantly elevated, but the systolic pressure fell to a level so low that the pulse-wave frequently became impalpable in the brachial artery, so that records of the blood-pressure could not be obtained. The fluctuations are recorded in Fig. 16. An X-ray taken on the 13th day showed an enlarged heart and an effusion at the right base, with encysted fluid above the transverse fissure. An electrocardiogram taken on the same day (Fig. 17a) showed sinus tachycardia with a rate of 125 per minute, low-voltage deflections, and inversion of the T wave in leads I, II, CR₄, and CR₇.

The oedema did not disappear completely until four weeks had elapsed. He was allowed to return home at the end of six weeks, since he was showing no further improvement. On discharge his heart was still enlarged, gross abnormalities were still evident in the electrocardiogram (Fig. 17b), and his toleration of exertion was very poor indeed. This man's illness was dominated by severe

myocardial damage, which showed very little improvement under treatment with aneurin. The diastolic pressure was abnormally high throughout the period of treatment, but owing to the extreme myocardial weakness the systolic pressure remained at a very low level. The lack of further progress towards the

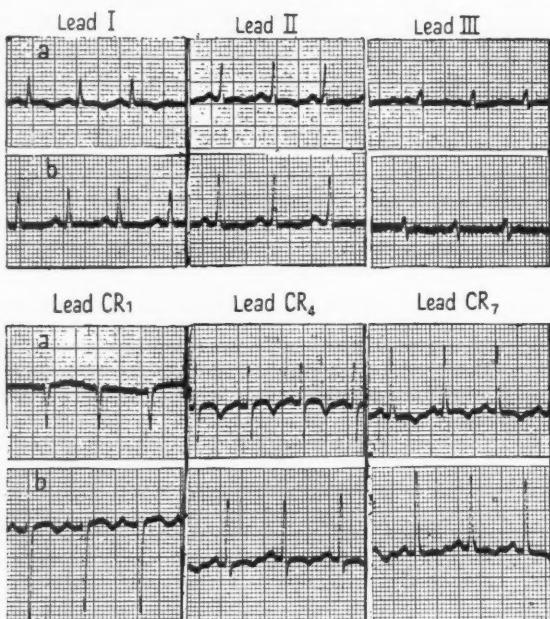


FIG. 17. Case 8. Electrocardiograms after (a) two weeks' treatment, (b) six weeks' treatment.

end of a prolonged period of intensive treatment suggested that the heart-muscle had sustained irreversible damage.

Case 9. Mohammed bin Ali bin Salim, aged 20 years. This youth, with his younger brother, had been at sea for two months on a voyage from Sokotra to Kuwait, where he hoped to seek his fortune. His diet had consisted only of rice, dates, and fish. Oedema of the legs appeared when he had been at sea for five weeks, and soon became generalized. On admission he showed firm oedema of the limbs and trunk, extending as high as the mid-point of the sternum. The gums showed profuse granulations round infected teeth, typical of scurvy. The heart showed no clinical or radiological evidence of enlargement, its sounds were of normal quality, and its resting rate was 84 per minute. The blood-pressure was 124/80. The chest appeared normal clinically and on X-ray. Moderate ascites was present, but the liver was not enlarged, and there was no other palpable abnormality within the abdomen. There were no signs of peripheral neuritis; on the contrary, the knee- and ankle-jerks were exaggerated, and the plantar responses extensor. Investigation showed a trace of albumin in the urine, with scanty granular casts; the blood showed 2.62 million red cells per c.mm., haemoglobin 7.7 gm. per 100 ml., and serum-protein 5.6 gm. per 100 ml. (albumin 2.8 gm., globulin 2.8 gm.), and the Kahn reaction was negative.

It is of interest that the younger brother showed a severe spastic paraplegia on admission, when he was unable to stand unsupported. He was not oedematous, but had scurvy of moderate severity. The spastic paraplegia responded rapidly to treatment with parenteral liver extract. Both brothers therefore

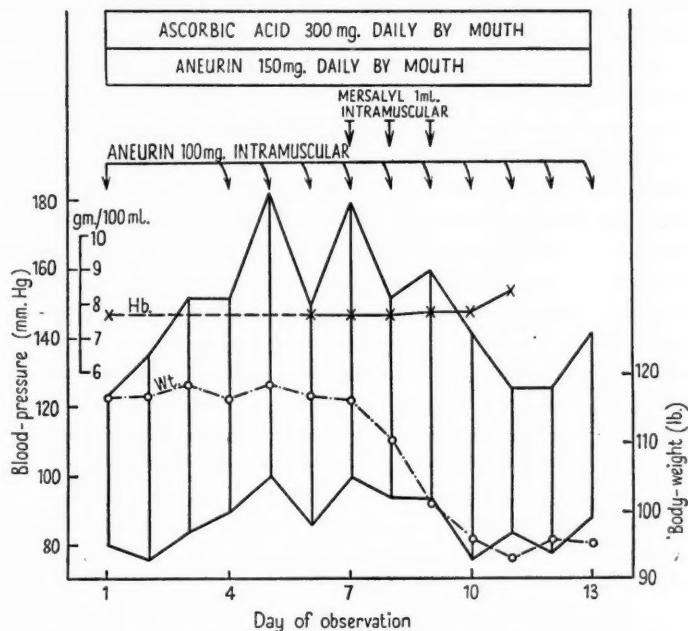


FIG. 18. Case 9. Mohammed bin Ali bin Salim. Blood-pressure, haemoglobin concentration, and body-weight.

showed the spastic type of nutritional spinal neuropathy, the lesion being more severe in the younger subject, who was still in the age of growth.

Treatment in Case 9 was initiated by an intramuscular injection of aneurin 100 mg., and he was given 150 mg. of aneurin daily by mouth, together with 300 mg. of ascorbic acid, with iron in addition. An injection of aneurin 100 mg. was repeated daily from the fourth to the 13th day. His response to treatment followed the same disappointing course as that seen in Cases 4 and 6. The oedema and the body-weight remained unchanged, while the blood-pressure rose rapidly to 182/100 on the fifth day (Fig. 18). After a transient fall on the sixth day it returned to 178/100 on the seventh, when the resting pulse- and respiration-rates also began to rise. In view of the danger of left ventricular failure, it now seemed essential to attempt other methods of promoting a diuresis, and he was therefore given an intramuscular injection of mersalyl 1 ml., which was repeated on the two subsequent days. A diuresis promptly ensued, the oedema subsided, and the blood-pressure fell, the reading on the 11th day being 126/84. Haemoglobin estimations were made on admission and daily from the sixth to the 11th day. The haemoglobin concentration showed no alteration until the 11th day, when it rose slightly. It may be inferred that the hypertensive response to aneurin was not determined by an increasing blood-volume, since no haemodilution occurred.

Discussion

Although the diagnosis of beri-beri was made mainly by exclusion, and was not supported by the demonstration of raised blood-pyruvate levels, for which facilities were not available, the assumption seems justifiable in view of the circumstances in which the outbreak occurred, and from the physical and pathological findings. The causation of this outbreak remains uncertain. All the men had worked in pearling ships previously, and several for many seasons, but all denied previous experience of such a condition. Some of them pointed out, however, that their diet in previous years had been supplemented at intervals with fresh meat and cheese. The rice forming the staple part of the diet was polished, while the dates would have contributed much carbohydrate but an inadequate amount of aneurin, of which their content is estimated only at 0.3 mg. per 1,000 non-fat calories (Nicholls, 1945). The climatic conditions which prevailed in the summer of 1951 were much more severe than for many years previously, and it is probable that the rice stocks held in the ships became heavily infected by a mould during a spell of unprecedented heat and humidity in the month of July. The destruction of 67.5 per cent. of the aneurin content of rice by some product of a mould, when cooked for 20 minutes, against a 30 per cent. loss in uncontaminated rice, was found by Cullinan, Kekwick, Watts, and Titman (1946) to be the cause of the outbreak of cardiovascular beri-beri among West African troops in Mauritius, to which reference has already been made. It is probable that our patients' diet, barely adequate in its aneurin/carbohydrate ratio in previous years, was this year grossly deficient through the lack of fresh vegetables and meat (aneurin content 0.7 to 5.0 mg. per 1,000 non-fat calories), and through the destruction of the greater part of the aneurin content of the rice by contamination with a mould.

The outstanding clinical manifestations were oedema, myocardial weakness, and arterial hypertension; signs of peripheral neuritis were minimal, and were quite overshadowed by the cardiovascular changes. The symptoms developed rapidly in a few days, and in the majority of the subjects epigastric pain accompanied the onset of the oedema. This pain was still present in most cases on admission, and was due to distension of the capsule of the liver; in those patients who responded to treatment it subsided rapidly as the size of the liver diminished. Oedema was found in all cases. Its character was tense, even hard, and it did not tend to shift with changes in posture. The oedema was generalized, involving, as well as the extremities, the trunk up to the middle of the sternum, and sometimes even to the clavicles. There was usually some swelling of the eyelids in addition. These findings accord with those of Smith and Woodruff (1951), and tend to distinguish 'wet beri-beri' from nutritional hypoproteinaemic oedema. In four patients there was also evidence of both pleural and peritoneal effusions; ascites alone was found in one patient, and pleural effusion without ascites in one. Hypoproteinaemia was not a factor in the production of this oedema, for the serum-albumin levels, which ranged from 2.8 gm. to 3.8 gm. per 100 ml., were well above the critical oedema level of 2 gm. per 100 ml.

(Walters, Rossiter, and Lehmann, 1947). Nor was oedema necessarily associated with cardiac failure, for Case 2 showed no signs of cardiac embarrassment. It is clear also that, although slight albuminuria, scanty casts, and a few cellular elements were found in the urine, these patients were not suffering from acute or subacute nephritis. That the oedema was due to aneurin deficiency seems undoubted. In Case 2 its mechanism appeared to lie in the peripheral vessels only; in the remainder cardiac failure provided an additional factor.

Myocardial weakness was not evident clinically in Cases 1, 2, and 9, although there was radiological evidence of left ventricular enlargement in Case 1. In the other patients there was clear evidence of myocardial disability on admission. The signs comprised: dyspnoea (5 cases); tachycardia (5 cases); enlarged area of cardiac dullness (4 cases); tic-tac rhythm (2 cases); gallop rhythm (2 cases); venous engorgement (3 cases); hepatic engorgement (3 cases); pulmonary oedema (2 cases). These abnormal clinical findings were supported by radiological evidence of cardiac enlargement, and by pathological changes in the electrocardiogram, in all six patients.

Arterial hypertension provided the most striking phenomenon in the series. A blood-pressure in excess of 150/90 mm. Hg was observed initially in four of the nine cases, and in all three patients of the additional group. A further rise in both systolic and diastolic pressures on treatment with aneurin was noted in two of the first four cases, and also in one of the additional group. Of the remaining five patients who showed no hypertension on admission, four developed a significantly raised blood-pressure within four days of the initiation of treatment. The single patient who did not show hypertension died within 24 hours of coming under treatment. The development of hypertension led directly to the death of one patient (Case 4), caused a dangerous attack of left ventricular failure in Case 6, and was the basis of severe cerebral symptoms in Case 1. Reference has already been made to previous reports of the association of hyperpiesis with cardiovascular beri-beri, but these reports have offered no explanation of its mechanism. The experimental work of Weiss and Wilkins (1937) has shown that cardiovascular beri-beri is characterized by a normal or increased velocity of blood-flow, a high venous pressure, and a reduced peripheral consumption of oxygen. The cardiac failure is, therefore, of the high-output type, and its basic mechanism combines general arteriolar dilatation with myocardial weakness. Treatment with aneurin leads rapidly to arteriolar constriction, which should relieve the burden on the labouring myocardium by reducing the venous return, provided no other factors are brought into play at the same time.

No detailed studies of changes in blood and tissue-fluid volumes, or of renal function, in cardiovascular beri-beri have yet been published. Such studies appear essential to the elucidation of the problem presented by the initial hypertension, and by the rising arterial pressure on treatment with aneurin, which were characteristic of the cases here described. Without alteration in the circulating volume, a general reduction in the arteriolar bed should result in a diminished cardiac output, so that only small alterations in arterial pressure should be provoked. It seems probable that two subsidiary mechanisms are

brought into operation, one involving the renal circulation and the other dependent on a reduction in the general capillary pressure. It is possible that gross generalized oedema, due to a raised filtration pressure, may induce an increased tension within the renal capsule, sufficient to obstruct the free flow of blood within the renal vessels. If aneurin were able to cause an acute arteriolar constriction before the oedema had dispersed, the result should be an enhanced degree of renal anoxia. Such a sequence of events could account for the early hypertension found in severely oedematous patients, and for the further rise in arterial pressure which has been seen to follow the administration of aneurin. As a result of the reduction in arteriolar dilatation, capillary pressure falls, and the withdrawal of fluid from the tissue-spaces by osmosis into the lumen of the vessels is thereby facilitated. This effect has been demonstrated by Weiss and Wilkins (1937) in three patients, in whom a diuresis occurred as the rate of blood-flow was reduced, though the osmotic pressure of the blood and the venous pressure remained unchanged. Under treatment with aneurin, therefore, the increased return of fluid from the tissue-spaces into the intravascular compartment should augment the circulating volume, and might well provide a further potent hypertensive factor in the presence of impaired renal secretion. Yet in Case 9 the indirect evidence provided by serial estimations of the haemoglobin concentration did not suggest that this had taken place.

In patients who have sustained severe myocardial damage, therefore, the therapeutic action of aneurin may do more than 'react in turn centrally on the heart in the same beneficial manner as the closing of an arterio-venous aneurism' (Weiss and Wilkins, 1937). It may in fact precipitate the failure of the left ventricle. It appears wise to control the rising arterial pressure with drugs of the methonium series until the myocardium has had time to return to a more healthy condition. At the time when our patients presented themselves for investigation, facilities were not available for estimations of blood-volume and thiocyanate space, or for detailed tests of renal function. A daily examination of the urine for total volume, specific gravity, and urea concentration did not help to explain the mechanism underlying the hypertension. In Cases 3 and 7 the specific gravity of the urine remained low throughout the phase of hypertension, and did not rise even after the weight had become stable. The urea concentration also showed little variation, remaining between 2.2 gm. and 2.4 gm. per 100 ml. in Case 3, and rising from 1.8 gm. to 2.2 gm. per 100 ml. in Case 7. In Case 4 the urine became scanty and more concentrated during the three days preceding death, but in Case 6 the specific gravity remained between 1.019 and 1.024 throughout the hypertensive period, and did not fall when this had subsided.

Electrocardiograms were taken on admission in Cases 3 to 8, and were repeated after treatment except in one patient (Case 5) who died shortly after admission. In addition to the standard limb leads, records were taken from the chest leads CR₁, CR₄, and CR₇. Each patient initially showed tachycardia with a sinus rhythm, but the deflections were of extremely low voltage. There was increase in the amplitude of the deflections after treatment in patients who showed a good clinical response to aneurin (for example, Case 7; Fig. 14). The

PR interval was normal, and the QRS interval was not prolonged except in Case 5 (Fig. 9). Abnormalities in the T waves were seen initially in Cases 4, 5, 6, and 8. These changes included (1) flattening or inversion of the T waves, and (2) elevation of the ST segments, which in some instances assumed a domed contour. The most striking abnormality was found in Case 5 (Fig. 9); this patient died 18 hours after the record was taken. In addition to sinus tachycardia, the QRS interval was prolonged to 0.12 seconds, and the changes in the T waves suggested a posterior infarction. These changes were most evident in lead III, in which there was considerable elevation of the ST segment, ending in sharp inversion. The electrocardiographic findings in the present series are in accord with those of Weiss and Wilkins (1937) and with the descriptions by East and Bain (1948); the changes are, however, of a more severe degree than those illustrated by the former authors. They are opposed to the statement made by Wenckebach in 1934, that in beri-beri the electrocardiogram is normal except in the conduction time, which is shortened.

Comment

The small outbreak of cardiovascular beri-beri here described lays emphasis on certain aspects of the disease which tend to be overlooked. The important points which emerge are:

1. The severity of the symptoms, and the acuteness of their onset;
2. The occurrence of arterial hypertension;
3. The persistence of myocardial damage in some cases long after recovery from the acute attack.

The degree of cardiac dilatation greatly exceeded that illustrated by Weiss and Wilkins (1937). This severity was undoubtedly attributable to the heavy physical stress to which the men were exposed during a period when they were living on a diet which, though adequate in total calories, was grossly unbalanced in respect of the aneurin/non-fat-calorie ratio. Arterial hypertension was a significant, even a dangerous, feature in eight of the nine cases under review. Although it has been noted previously as an occasional complication of beri-beri, our experience suggests that there exists a direct causal relationship between them. The ultimate prognosis is stated by most authorities (Price, 1950; Manson-Bahr, 1950; Weiss and Wilkins, 1937) to be complete recovery, provided that the patient survives the early phase of acute cardiac failure. It appears probable, however, that in at least a few cases irreparable myocardial damage may persist, in spite of recovery from the acute stage of cardiovascular failure. Case 8 illustrates this point.

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Summary

1. Examples of severe cardiovascular beri-beri occurring among pearl divers in the Persian Gulf are described.
2. Arterial hypertension, which increased on treatment with aneurin, was the outstanding clinical feature.
3. Permanent myocardial damage was observed in at least one patient who survived.
4. Possible mechanisms of the hypertension are discussed. The suggestions made are tentative, and further investigation is required before firm conclusions can be drawn.

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RADIATION NEPHRITIS¹

By REGINALD W. LUXTON

(From the Christie Hospital and Holt Radium Institute, Manchester)

With Plates 18 to 20

THE purpose of the present paper is to describe the clinical and clinico-pathological features of the nephritis which may be produced when the kidneys are included within radiotherapeutic fields in man. For 25 years it has been known that severe nephritis, closely resembling human chronic nephritis, can be produced experimentally in animals by X-radiation of the kidneys (Hartman, Bolliger, and Doub, 1926; O'Hare, Altnow, Christian, Calhoun, and Sosman, 1926). Radiotherapists have believed, however, that the kidneys are relatively immune to doses of X-radiation within the scope of routine therapy, although renal damage has been recognized in isolated cases after exposure to high doses of X-rays or radium. Hence fear of resulting damage to the kidney has not set a limit to X-radiation of the abdomen.

The usual treatment of seminoma is surgical removal of the affected testis followed by a course of X-ray treatment of the posterior abdominal lymph-glands, which are generally the first site of metastasis. Seminoma tissue is very sensitive to X-rays, and a high proportion of cures is attained by the foregoing method (Boden and Gibb, 1951). At the Christie Hospital and Holt Radium Institute, Manchester, an alteration in the technique of X-ray treatment for seminoma was made in 1948, the details and implications of which, from the aspect of the radiotherapist, were considered by Kunkler, Farr, and Luxton (1952). The essence of the changed technique was that, whereas previously only limited volumes of both kidneys were included within the radiotherapeutic field, the new method involved irradiation of the whole of both kidneys by a dose of at least 2,300 r during a period of five weeks. The possibility of renal damage by this treatment was first considered when a patient was found to have severe hypertension, commencing seven months after radiotherapy. He was extremely ill for several months, but eventually recovered sufficiently to return to normal life, although with evidence of residual chronic nephritis. Other cases developed later. The present paper is founded on a clinical study of 27 patients with X-ray nephritis, some of whom have been under observation for more than two years, and on autopsy studies of four of the seven who died. During the four years from 1947 to 1950 the total number of men given abdominal radiotherapy for testicular tumours at the Christie Hospital and Holt Radium Institute was 137. The great majority of patients were aged between 20 and 50 years. Prior to radiotherapy the blood-pressure was rarely recorded, and in many cases

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there is no record of urinary examination. Although it has not been possible to follow up some of the patients, 27 are known to have had albuminuria subsequently, and associated hypertension, often severe, has been found in 25. There is thus evidence of renal damage in at least 20 per cent. of the patients treated. Of the 27 patients under consideration, 13 developed acute symptoms of nephritis within a period of six to 12 months from the start of radiotherapy, and five died. Those who survived the acute phase were left with signs of chronic nephritis. In 12 other patients the renal damage, though not producing serious symptoms, was readily discovered by clinical examination. On this basis, and in the absence of the history of radiotherapy, one would have classified seven of the 12 cases as chronic glomerulonephritis, four as benign essential hypertension, and one simply as albuminuria or latent nephritis. The remaining two of the 27 cases presented clinically as fulminating malignant hypertension, arising at a long interval after radiotherapy. On this clinical basis the 27 cases will be described as acute radiation nephritis (13 cases), chronic radiation nephritis (eight cases), benign hypertension (four cases), and late malignant hypertension (two cases).

Acute Radiation Nephritis

Thirteen patients presented either a history, or signs and symptoms, of what can be described as acute radiation nephritis, and details are given in Table I. Two patients were examined by the author within one month of the onset of symptoms, and eight within three months. In most instances the course of the disease has been studied for many months, and one patient has been under observation for three years.

Latent period. A latent period of six to 12 months, estimated from the start of radiotherapy, elapsed before the onset of symptoms attributable to the kidney. The duration of the latent period in the 13 cases was as follows: six months (two cases); seven months (one case); eight months (six cases); nine months (three cases); 12 months (one case). During the latent period there were no symptoms, except nocturia in a small minority of patients, a disability not troublesome and not necessarily renal in origin. The patients were able to return to work after convalescence from radiotherapy.

Symptoms and signs. The onset of symptoms was gradual, but most patients were incapacitated within a month. There was no preceding sore throat or other infection. The earliest symptom was one of the following: oedema (five cases); dyspnoea on exertion (five cases); hypertensive headache (one case); nocturia (one case); lassitude and vomiting (one case). The main clinical features observed in the 13 patients were as follows: oedema (11 cases); urinary changes (all cases); hypertension (all cases); headache (10 cases); retinitis (five cases); anaemia (all cases); cardiac enlargement (all cases); dyspnoea (12 cases); nausea and vomiting (eight cases); lassitude (seven cases); nocturia (seven cases); drenching sweats (three cases); left ventricular failure (four cases); hypertensive encephalopathy (two cases); terminal chronic uraemia (three cases); congestive heart failure (four cases).

Oedema. Eleven patients showed oedema. In six patients, none of whom died, the oedema was confined to the legs. All the five patients who died had oedema in regions other than the legs at some time during their illness, and all five had serous effusions into pleura and peritoneum. Only three patients had oedema of the face due to nephritis; one other patient showed facial oedema after a blood transfusion. Generalized oedema at the onset of symptoms occurred in two patients only (Cases 2 and 4), but Case 7 developed generalized oedema at a later stage. Two patients (Cases 6 and 11) with severe renal damage never showed oedema, although both had severe hypertension, anaemia, and azotaemia.

Urinary changes. Albuminuria was persistent in all the patients, the amount varying between 0.5 gm. and 4 gm. per litre (Esbach). The urinary specific gravity was usually below 1,012, but some patients had no serious impairment of their ability to concentrate urine. Oliguria was never observed after the patient was admitted to hospital, except in association with congestive heart failure. In no case did haematuria occur at any time. In nine cases epithelial, hyaline, or granular casts were found in the urine, and a few red blood-corpuscles were seen in two cases.

Hypertension. The blood-pressure varied considerably from patient to patient. Ten patients had a systolic pressure of 170 mm. Hg or over at the first clinical examination, and the diastolic pressure was raised in proportion. In two patients (Cases 2 and 8) the blood-pressure was within the accepted normal range until several weeks after the onset of renal symptoms. On the other hand the initial systolic pressure in three cases was over 200 mm. Hg. Case 6 was referred to me with a diagnosis of 'cerebral metastases' on account of intense headache, vomiting, papilloedema, and retinitis; the symptoms were due to hypertension. In seven of the eight patients who survived the acute stage of the disease, clinical improvement was accompanied by a fall of blood-pressure below 150/100 during an average period of 16 months from the onset of symptoms (limits six months and 30 months). In most of these patients the blood-pressure was at its highest level within six months of the first symptom.

Headache typical of hypertension occurred in 10 patients. Its onset was usually later than the oedema or effort dyspnoea, and it was the initial symptom in only one patient. Symptoms occasionally associated with the headache were nausea, vomiting, flushing of the face and neck, and photophobia.

Retinitis was observed in five patients (Cases 3, 4, 6, 7, 11) of whom three died. The retinae showed recent white exudates, haemorrhages, and papill-oedema.

Anaemia. Table I shows that in the eight patients examined within three months of the onset the haemoglobin when first recorded was 55 per cent. or less. The blood picture was that of a severe normochromic normocytic anaemia. The leucocyte counts, total and differential, were normal, as were the coagulation time, bleeding time, serum-bilirubin, and reticulocyte counts. The blood-platelets also were normal except in the later stages, when thrombocytopenia and purpura occurred. Sternal marrow studies in nine patients revealed an

TABLE I
Acute Radiation Nephritis

Case number	Age (years)	X-rays: Total dose and duration	Latent period in months	Main symptoms	Clinical examinations	Interval (months) from first symptom to first examination	Interval (months) between first and last examinations	Urine			Clinical course	
								First	Last	Albumin		
1	35	2,900 r	8	Headache Dyspnoea Latitude Nocturia Vomiting	Blood-pressure Blood-urea Haemo-globin Renal function	1	183/90	155/100	17	+	1,010	Epithelial casts
2	40	3,000 r	37 days	Headache Dyspnoea Oedema Vomiting	Blood-pressure Blood-urea Haemo-globin Renal function	1	145/90	195/110	24	++	1,010	Hypertension, anaemia, and renal failure began 8 months after start of radiotherapy, and were greater 12 months after start. Patient required repeated transfusions. Slowly improving. Residual chronic nephritis
3	29	3,000 r	35 days	Dyspnoea Oedema Latitude Headache Retinitis Vomiting	Blood-pressure Blood-urea Haemo-globin Renal function	2	170/80	160/110	2	++	1,010	Hyaline and granular casts.
4	32	3,000 r	37 days	Oedema Headache Dyspnoea Latitude Vomiting Retinitis	Blood-pressure Blood-urea Haemo-globin Renal function	2	165/85	190/110	3	++	1,010	Hyaline and granular casts
5	52	3,000 r	40 days	Dyspnoea Oedema	Blood-pressure Blood-urea Haemo-globin Renal function	2	190/95	210/110	1
6	32	3,250 r	32 days	Dyspnoea Headache Amaurosis Retinitis Vomiting	Blood-pressure Blood-urea Haemo-globin Renal function	3	205/125	150/100	34	None	1,010	No casts. Few red cells
7	38	3,000 r	29 days	Dyspnoea Oedema Headache	Blood-pressure Blood-urea	3	200/115	210/130	9	..	1,010	No casts
												Died 12 months after onset of symptoms. Left ventricular failure. Terminal hypotension. Transient cerebral oedema. Epilepsy.

Renal function	Age	Sex	Initial symptoms	Onset	Initial blood pressure	Initial casts	Initial haematuria	Initial proteinuria	Initial oedema	Initial renal function	Final renal function	Final blood pressure	Final casts	Final haematuria	Final proteinuria	Final oedema	Final renal function	Final blood pressure	Final casts	Final haematuria	Final proteinuria	Final oedema	Final renal function
22-0	7	38	3,000 r 29 days	8	Dyspnoea Oedema Headache Retinitis Nocturia Lassitude Vomiting	3	Hypotension-Blood-urea Haemo-globin-Renal function	200/115 124 44%	210/130 94 48%	+	1,010	No casts	Died 12 months after onset of symptoms. Left ventricular failure. Terminal hypotension, encephalopathy with retinitis and epilepsy. Transfusion reactions troublesome.										
8	30	3,000 r 32 days	6	Dyspnoea Oedema Nocturia	3	Blood-pressure-Blood-urea Haemo-globin-Renal function	140/70 60 50%	110/60 30 83%	Slight oedema of legs only	11	+	1,010	Granular and hyaline casts	Mild anaemia required repeated transfusions at first only. Considerable improvement during 12 months' observation. He is at work									
9	36	3,000 r 36 days	6	Oedema Dyspnoea Lassitude Headache Nocturia	4	Blood-pressure-Blood-urea Haemo-globin-Renal function	220/110 80 50%	145/95 46 76%	Slight oedema of legs only	16	+	1,010	Granular casts	Moderately severe renal failure. Severe hypertension and moderate renal failure began 6 months after start of radiotherapy. Repeated blood transfusions. Hypertension persisted for 9 months. Illustrates the considerable degree of recovery possible from fairly severe acute radiation nephritis									
10	36	3,000 r 35 days	9	Dyspnoea Headache Vomiting Lassitude Nocturia	4	Blood-pressure-Blood-urea Haemo-globin-Renal function	190/115 74 50%	170/110 36 78%	Slight oedema of legs only	11	+	1,010	Hyaline casts	Moderately severe case. Slowly improving. Anæmia refractory. Sharp reaction to first blood transfusion, with rise of blood-urea from 35 mg. per 100 ml.									
11	33	3,000 r 35 days	9	Headache Lassitude Retinitis Nocturia Vomiting	5	Blood-pressure-Blood-urea Haemo-globin-Renal function	195/95 89 42%	180/100 105 21%	None	11	++	1,010	Granular casts	Severe hypertension, with retinitis, renal failure, and anæmia, began after latent period of 9 months. Repeated blood transfusions. Symptoms of acute radiation nephritis abated after 6 months. Severe residual chronic nephritis, probably slowly progressive. Patient is ambulant									
12	48	3,000 r 35 days	8	Oedema Dyspnoea Headache	9	Blood-pressure-Blood-urea Haemo-globin-Renal function	175/110 60 44%	145/90 70 68%	Oedema of legs only	15	+	1,010	No casts	Initial symptoms due to hypertension and anæmia. Repeated blood transfusions. Blood-pressure normal after 9 months. Hypertension level persists at 70 mg. per 100 ml. He is back at work and free of symptoms									
13	24	3,000 r 33 days	8	Oedema Nocturia	9	Blood-pressure-Blood-urea Haemo-globin-Renal function	170/105 40 46%	150/70 43 46%	Slight oedema of legs only	15	+	1,015	Epithelial and hyaline casts	Symptoms mild. Moderate anæmia required blood transfusions at first only. Hypertension greatest about 12 months after onset of symptoms, later returning to normal. Variable blood-urea, with sharp increase during intercurrent infection. Patient is at work									

Renal function: 'Normal' or 'Impaired' relates to urea concentration test. Percentage relates to urea clearance test. **Blood-urea in mg. per 100 ml.**

active marrow. The erythroid series was normoblastic, but the nucleated red cells showed much variation in form and size in some cases. The anaemia was completely resistant to all forms of therapy except blood transfusion. In the 13 patients three variations in the course of the anaemia were seen. The five fatal cases showed rapid progress of the anaemia in spite of treatment. Five patients (Cases 6, 8, 9, 10, and 13) required blood transfusions during the first few months, but subsequently remained stabilized at a haemoglobin level above 60 per cent. In the remaining three patients (Cases 1, 11, and 12) the refractory anaemia has persisted for two years or more, requiring repeated blood transfusions.

Renal function tests. Urea clearance and urea concentration. Table I indicates the varied degrees of impairment of renal function occurring in these cases. It is noteworthy that at the first examination the urea clearance was below 25 per cent. in five cases. In some patients renal function improved along with the clinical condition. One patient (Case 6) at the fifth month after the onset of symptoms had a urea clearance of 18 per cent., which increased to 61 per cent. at the 36th month.

Blood-urea. The blood-urea level was over 80 mg. per 100 ml. in nine patients at the first examination. The blood-urea in the remaining patients (Cases 8, 10, 12, and 13) was between 40 and 75 mg. per 100 ml. at the first examination. In the five patients who died the blood-urea exceeded 100 mg. per 100 ml. at some time during the first three months of the illness. After the acute stage the blood-urea remained at a level well above normal in some patients, and in others its level fell gradually for many months. In the three patients (Cases 1, 11, and 12) in whom the blood-urea was usually at a level between 70 and 120 mg. per 100 ml., repeated blood transfusions were required. Five patients (Cases 6, 8, 9, 10, and 13) who required blood transfusion during the acute stage, were able to manage without further transfusion when the blood-urea level had become stabilized below 60 mg. per 100 ml. Two extraneous factors caused a transient increase in the blood-urea. Case 13 had a sharp intercurrent infection, characterized by a rigor, pyrexia, headache, and leucocytosis. The cause was never established, but the blood-urea, previously stabilized at 50 to 60 mg. per 100 ml., increased to 112 mg. per 100 ml. during the pyrexia. Several observations of the blood-urea were made in relation to the transfusion of whole blood. If the transfusion was uneventful no significant increase in the blood-urea resulted from it. A sharp increase in the blood-urea occurred in two patients during transfusion reactions.

Clinical course. Five of the 13 patients died, four within five months of the onset of symptoms and one after 12 months. In a severe case the natural progress of the disease led to congestive heart failure, left ventricular failure, hypertensive encephalopathy, and uraemia. A combination of the symptoms of these conditions was seen in all the fatal cases. The patients who recovered began to improve about six months after the onset of symptoms. Although chronic nephritis has remained in every case, a considerable degree of recovery has been observed, shown both clinically and by tests of renal function.

Prognosis. Early signs which proved of value in prognosis were the severity of the oedema and the blood-urea level. The eight patients who survived had oedema of the legs only, whereas all those who died had serous effusions with or without generalized oedema. The blood-urea in all the fatal cases was over 100 mg. per 100 ml. at some time during the first three months after the onset of renal symptoms; but one patient who recovered (Case 1) also had a blood-urea above that figure during the first three months. The blood-pressure alone was not a good guide to prognosis, but increasing hypertension accompanied by progressive anaemia and a rising blood-urea was a dangerous syndrome. Retinitis occurred in five patients only, all severely affected, of whom three died. The retinitis in the two patients who recovered (Cases 6 and 11) was extensive, causing amaurosis in Case 6. Factors which seemed to have no prognostic importance were the latent period, the age of the patient, the blood-pressure in the early stages of the disease, and renal function tests during the first five months.

Treatment. Two methods of treatment kept certain patients alive until the active phase of the disease had subsided, namely, rest in bed and repeated blood transfusions. A lessening of dyspnoea, oedema, and headache, with reduction in blood-pressure and improvement in retinal appearances, was seen from rest in bed alone. The anaemia was completely refractory to the following preparations, used singly and in combination: intravenous iron, vitamin B₁₂, folic acid, proteolysed liver, intramuscular liver extract, vitamins A, B, C, and D, and ACTH. Blood transfusion was the only effective means of sustaining the patients' haemoglobin, thereby reducing the liability to hypertensive and congestive heart failure. Special care was required in cross-matching and in the administration of blood, for reactions, both biological and mechanical, were frequent. Restriction of fluid and salt was useful in checking oedema. For pulmonary oedema, cardiac asthma, and chronic uraemia, treatment was symptomatic.

Chronic Radiation Nephritis

When the acute stage of radiation nephritis had subsided, the clinical condition remaining showed close resemblance to chronic glomerulonephritis. The blood-pressure usually fell considerably, but moderate hypertension sometimes persisted. A routine examination of other men who had been given abdominal radiotherapy after orchidectomy for seminoma revealed that several had albuminuria, and some showed signs of chronic glomerulonephritis. Table II indicates the main features of eight such cases (Cases 14 to 21). None of these men gave a history or other evidence of acute radiation nephritis, and in seven the condition was revealed only by examination, for they had no symptoms. Their age varied between 17 and 60 years. In no case was there a history of nephritis or preceding hypertension, nor was there any familial tendency to hypertension. The total X-ray dosage in all cases was 3,000 r during a period of about 35 days. The severity of the nephritis varied from patient to patient, but the usual clinical and clinico-pathological features were seen in most—

hypertension, albuminuria, anaemia, reduction of urinary specific gravity, and impairment of renal function as revealed by the standard tests. Intravenous pyelography was normal in four cases, and showed impaired concentration in two. Granular, epithelial, or hyaline casts were found in the urine of four patients. The blood-cholesterol was within normal limits, and where tests were made there was no major abnormality in serum-sodium or serum-potassium. The albumin/globulin ratio tended to be low. The renal condition has been kept under observation for approximately 14 months in seven of the eight patients, and there has been no clear clinical or biochemical evidence of improvement or deterioration. The blood-urea in each patient, although sometimes normal, was sometimes raised (40 to 100 mg. per 100 ml.). Such variations in the blood-urea were unrelated to blood-pressure and haemoglobin estimations made at the same time.

Benign Hypertension

On purely clinical grounds, four patients in middle life would be accepted as suffering from benign essential hypertension (Cases 22, 23, 24, and 25). In each case the main abnormality was a persistently raised blood-pressure, without any evidence except slight albuminuria to indicate the cause. As will be seen from Table II, renal function tests were normal, there was no reduction in ability to produce a concentrated urine, and no anaemia. The retinae were normal apart from some arterial hypertrophy. Blood-urea estimations in the four cases (a total of 24 estimations) tended to be at the upper limit of normal or slightly raised. A long interval had elapsed from the start of radiotherapy in all four (62 months, 44 months, 42 months, and 31 months). Observation for a period of nine to 14 months has shown no tendency to major alteration in blood-pressure. It is unfortunate that the blood-pressures were not recorded prior to radiotherapy. A study of the periodic chest radiographs suggests, however, that in three cases the beginning of the hypertension was six to 12 months after the start of radiotherapy (see the section on cardiac enlargement, p. 224). None of the patients gave a history suggesting acute radiation nephritis except that, on questioning, Case 22 admitted to a period of rather exceptional dyspnoea of effort beginning about six months after his X-ray treatment. There was no other associated symptom, and he had continued at work without interruption. It may be significant that Cases 22 and 23 received a smaller total dosage of X-rays than any patient in the whole series. Case 22 had been given 2,500 r during 23 days, and Case 23, 2,230 r during 22 days. The only comparable dose in the series was in Case 26, who was given 2,600 r during 27 days, and died 19 months later of fulminating malignant hypertension.

Malignant Hypertension from X-radiation

Two patients (Cases 26 and 27) were seen at a long interval after radiotherapy, with a syndrome resembling malignant hypertension of a fulminating type. In both patients a long period of apparently good health followed the abdominal

TABLE II
Chronic Radiation Nephritis

Case number	Age (years)	Time (months) since start of radiotherapy	Blood-pressure range	Haemoglobin (%) range	Urine		Intravenous pyelogram		Test of renal function		Cardiac enlargement and interval from start of radiotherapy		Clinical syndrome	
					Albumin	Specific gravity	Casts	Impaired concentration	Urea clearance since 20%	Slight (left ventricle); 30 months				
14	38	34	175/100–130/80 (21 tests)	50–84 (21 tests)	+	1,010	Absent							Chronic glomerulonephritis
15	31	25	170/90–135/80 (12 tests)	39–92 (12 tests)	62–72	++	1,010	Epithelial and hyaline	Slightly impaired concentration	Moderate (left ventricle); 24 months				Chronic glomerulonephritis
16	45	48	170/70–155/80 (7 tests)	35–58 (7 tests)	61–70	Trace	1,010–1,016	Granular and red cells						Chronic glomerulonephritis
17	35	20	150/80–120/70 (10 tests)	39–73 (10 tests)	58–74	+	1,010–1,013	Granular and hyaline	Urea clearance 56%					Chronic glomerulonephritis
18	60	32	190/100–175/90 (6 tests)	34–48 (6 tests)	70	+	1,012	Absent	Normal	Moderate impairment of urea concentration	Slight (left ventricle); 24 months			Chronic glomerulonephritis
19	34	18	180/85–150/60 (9 tests)	25–60 (9 tests)	64–80	+	1,014	Absent	Normal	Slight impairment of urea concentration				Chronic glomerulonephritis
20	39	38	170/100–130/75 (5 tests)	34–60 (5 tests)	74–90	++	1,016	Absent	..					Chronic glomerulonephritis
21	17	23	120/70–90/50 (7 tests)	30–48 (7 tests)	80	+	1,018–1,030	Hyaline	..					Latent nephritis
22	35	62	225/140–180/120 (10 tests)	28–52 (10 tests)	90	Trace	1,015	Granular	Normal	Urea clearance 90%	Slight: 6 months; Moderate: 11 months.			Benign hypertension
23	50	31	205/120–185/100 (9 tests)	28–52 (9 tests)	90	+	1,020	Granular	Normal		Moderate; 58 months			Benign hypertension
24	42	44	185/105–165/90 (3 tests)	18–38 (3 tests)	86	Trace or +	1,015	Hyaline	Normal		Moderate; 8 months.			Benign hypertension
25	49	42	170/95–170/100 (2 tests)	41–52 (2 tests)	106	+	1,024	Absent	..	Urea clearance 106%	Moderate; 8 months.			Benign hypertension

radiotherapy, symptoms of renal damage beginning after 18 months in one case and 24 months in the other. Deterioration was thenceforth extremely rapid, and both died within seven weeks. Case 26 was examined within two weeks of the beginning of symptoms, and although severe hypertension, retinitis, and albuminuria were discovered, the blood-urea was normal, and ability to produce a concentrated urine was not impaired. Only slight anaemia was present at this stage. Along with hypertensive encephalopathy, terminating in a brain-stem haemorrhage, there appeared a rapidly progressive normochromic anaemia, which in three weeks diminished the haemoglobin from 72 per cent. to 42 per cent. During the same time the blood-urea rose from 38 mg. to 85 mg. per 100 ml. Purpuric haemorrhages in the skin and from the gums appeared at a time when the blood-urea was relatively little raised. Case 27 was more advanced in this terminal illness when admitted to hospital, having had symptoms for three weeks, and he died a week later. On admission the clinical picture was that of severe hypertension with bilateral papilloedema, retinal haemorrhages and exudates, gross albuminuria with renal failure (blood-urea 154 mg. per 100 ml.), and severe normochromic anaemia (haemoglobin 39 per cent.). A study of chest radiographs in these two cases suggests that cardiac enlargement did not develop until the last few weeks. I suspect, however, in spite of the absence of symptoms, that hypertension had been present for a longer period, for a few sharply demarcated white exudates were visible on the retina of Case 26, and autopsy of Case 27 revealed a heart weighing 625 gm.

Cardiac Enlargement in Radiation Nephritis

An accidental circumstance sheds light on the evolution of the different clinical types of radiation nephritis. To detect lung metastases from a seminoma, chest radiographs are taken before treatment and repeated from time to time during the 'follow-up'. Enlargement of the heart was noted in some of the radiographs, and subsequent comparison of successive films from each patient has given information about the course of his nephritis. In acute radiation nephritis cardiac enlargement occurred between the sixth and tenth months after the start of radiotherapy, and was therefore usually present at the time of the first symptom. The enlargement was generalized, not affecting the left ventricle alone, and is attributed to the combined effects of severe anaemia and hypertension. In all the patients who recovered, a reduction in size of the heart followed the improvement in blood-pressure and anaemia (Plate 18, Fig. 1). This observation suggests that the enlargement was due mainly to dilatation. In the four patients found to have benign hypertension, cardiac enlargement was first evident in radiographs taken six to nine months after the start of radiotherapy. In three of the patients the enlargement was considerable, and has persisted (Plate 19, Fig. 2). The enlargement was generalized when first seen, but eventually resolved into enlargement mainly of the left ventricle. Increase in size and density of the aorta were also visible. Radiographs of the two patients in whom late malignant hypertension was found suggest that

cardiac enlargement may have been of relatively late development. Case 26 had no cardiac enlargement at the sixth month, and only slight left ventricular hypertrophy at the 19th month, when his blood-pressure was 250/110. Case 27 showed no cardiac enlargement at the fifth and ninth months, but a moderate generalized enlargement at the 25th month. In the patients with chronic radiation nephritis cardiac enlargement, when present, took the form of left ventricular hypertrophy in keeping with the degree of hypertension. It is noteworthy that neither history nor chest radiographs suggest a preceding acute phase in chronic radiation nephritis.

Pathology

Autopsies were performed in four cases; in three the clinical diagnosis was acute radiation nephritis (Cases 3, 4, and 5), and in one (Case 27) late malignant hypertension. In Case 4 permission was given for a limited autopsy only. Effusion of clear or straw-coloured fluid was usually present in the peritoneum and pleura. Fibrinous pericarditis was found in two cases, and intrapericardial haemorrhage in one. The heart showed moderate enlargement, affecting especially the left ventricle, in the three cases of acute radiation nephritis; the valves and coronary arteries were normal. The heart in Case 27 weighed 625 gm.; the heart-muscle was histologically normal. Some increase of fibrous tissue was noticed in the capsules of the liver and spleen, and also in sections of the liver and pancreas, but no other histological change was seen in these organs. The stomach showed mucosal atrophy in one case of acute radiation nephritis. No abnormality could be found in the small bowel except adhesion between adjacent loops (Case 27). In no case were seminoma metastases discovered. Lymph-nodes in the abdomen and elsewhere were inconspicuous. The renal pelvis, ureters, and bladder were normal, but in Case 4 a little periureteric fibrosis was observed at the level of the aortic bifurcation. In all the patients a layer of moderately dense fibrous tissue was seen to separate the kidneys and suprarenals from the peritoneum, but the renal capsule stripped fairly easily. The kidneys were normal in size and external appearance except in Case 4, in whom they were enlarged and showed abnormalities in the cortex, and in Case 3, who had a symmetrical horseshoe kidney with two ureters.

Plates 19 and 20 (Figs. 3 to 7) depict the main histological features in the kidneys. In brief, the four cases show certain features in common: (1) There is marked fibrous thickening of the renal capsule. (2) Almost all glomeruli are abnormal to some degree, the consistent change being ill-defined hyaline obliteration of capillary loops. (3) Intertubular fibrosis is widespread, and the tubules are mainly atrophic. (4) Fibrinoid necrotic lesions of arterioles or intralobular arteries are present in varying amount. Arteries of arcuate size show no gross ischaemic changes. The overall picture most nearly resembles malignant nephrosclerosis, but differs from this condition in the following significant details: (1) Almost all glomeruli are damaged. (2) There is generalized intertubular fibrosis. (3) Capsular fibrosis is remarkable. (4) There is no evidence of long-standing hypertension in the larger arteries.

Discussion

Radiation nephritis in experimental animals. Nephritis can be produced readily by X-radiation in the experimental animal. Hartman, Bolliger, and Doub (1926, 1927) described the condition in dogs, and pointed out that a condition very closely resembling chronic nephritis in man can be induced in the dog by X-radiation. About the same time O'Hare, Altnow, Christian, Calhoun, and Sosman (1926) carried out experiments on rabbits. The right kidney was brought up into a flank incision and X-radiation was given, so that eventually it was possible to compare the irradiated right kidney with the normal left kidney. These observers noticed that with small doses of X-rays given for short periods only slight histological changes occurred, but with higher doses given over a long period chronic sclerotic changes of a severe nature could result.

Human radiation nephritis. Nephritis due to X-radiation in human beings has rarely been recorded. In this connexion the comment of Hall and Whipple (1919), 'If there is renal injury it is of relatively slight grade and is not a constant finding', sums up the general opinion of radiotherapists. During recent years, however, a few cases have been described. Dean and Abels (1944) described the case of a woman who at the age of 20 years, when the kidneys and blood-pressure were apparently normal, received radiation in the left upper quadrant of the abdomen. Seven years later she suffered from severe headaches, the blood-pressure was high, and the left kidney was radiologically abnormal. Functional tests showed a normal right kidney and a grossly deficient left kidney. After surgical removal of the sclerotic left kidney the blood-pressure became normal, and remained so. The most recent reference to the condition in man is by Zuelzer, Palmer, and Newton (1950). They described the clinical and histological features in three children, all under five years of age, who had been given deep X-ray therapy to the kidney regions on account of a malignant tumour, either renal or in adjacent structures. Relatively large doses of X-rays were used (5,200 r to 6,850 r). In all three children symptoms of nephritis developed within six months of the commencement of radiation, and all died of renal failure and hypertension within seven months of the commencement of radiation. The authors stated that the renal lesions were unique in appearance, and interpreted them as evidence of injury to the endothelium and basement membrane of the glomerular capillaries and Bowman's capsules. Tubular atrophy, degeneration, and necrosis, and interstitial fibrosis were also found. The authors commented that 'review of the literature is far from conclusive in regard to harmful effects of therapeutic radiation in the kidneys'. Their histological illustrations show features identical with those described in the present paper. There is now no doubt that serious and even fatal renal damage may result from X-radiation of the kidneys with dosages within accepted therapeutic limits. Radiation nephritis must be considered in any man who has been treated for seminoma testis by orchidectomy and abdominal X-radiation, and in whom signs or symptoms of nephritis or of hypertension subsequently arise. It is probable that the kidneys are always damaged to some extent by deep

radiotherapy involving the renal areas, with resulting renal symptoms in a few patients and asymptomatic nephritis in others. The series of cases of radiation nephritis here described came to light because a slight alteration in technique caused the whole of both kidneys to be irradiated, a procedure which seems greatly to diminish the renal reserve. There are two main reasons why acute radiation nephritis has hitherto escaped clinical recognition. The clinical effects of renal damage may arise so late after the radiotherapy that the cause is unsuspected; and the conditions for which radiotherapy is given are usually so serious that life is much curtailed, and symptoms arising long after the treatment are usually attributed to the disease.

Pathogenesis. Radiation nephritis is the reaction of a highly differentiated organ to an unusual type of injury. It is hard to say how much the damage to nephrons is due to direct injury by X-rays, and how much it is secondary to vascular damage or to the widespread interstitial fibrosis. During the course of radiotherapy hyperaemia of the kidneys and other irradiated structures is probable, and its degree, like the skin reaction, may vary in different patients. It seems possible that an excessive tissue reaction during radiotherapy may be followed by fibrosis. The latent period of eight to 12 months is roughly the same as in the central nervous lesions caused by radiotherapy (Boden, 1948). A point of special interest concerns the increase of fibrous tissue in the renal capsules. Page (1939) has described a fibrous perinephritis, caused by wrapping cellophane round the kidneys of experimental animals, resulting in severe and persistent arterial hypertension. Renal ischaemia is thus produced by a method different in principle from that involved in clamping of the renal arteries. It is possible, therefore, that a constrictive perinephritis may cause hypertension in man. Thickening of the capsule was a constant finding in the four cases of radiation nephritis which came to autopsy in the present series; but the capsules were not densely adherent, nor were the kidneys obviously compressed.

Clinical features. From the clinician's standpoint three matters need further consideration: the relationship between acute radiation nephritis and acute Bright's disease; hypertension in radiation nephritis; and anaemia in radiation nephritis.

1. *Relationship between acute radiation nephritis and acute Bright's disease.* In giving the name acute radiation nephritis to the syndrome described in this paper, certain relationships must be emphasized. First, although the severer cases show resemblance to acute Bright's disease, acute radiation nephritis has its own distinctive clinical and pathological features. Again, the disease is the result of previous radiotherapy, and the time-relationship between radiotherapy and renal symptoms is remarkably constant. Lastly, the condition bears a basic resemblance to chronic radiation nephritis arising insidiously, the acuteness being due to the intensity of symptoms common to both, especially hypertension and anaemia. Some cases of acute radiation nephritis show a general clinical resemblance to acute Bright's disease. A further similarity lies in the probable damage to every nephron in both diseases. In acute radiation nephritis the technique of radiotherapy makes such damage possible, and the

histological findings lend support to the suggestion. The clinical pictures of acute radiation nephritis and acute Bright's disease, however, differ in important respects. Haematuria was not observed in acute radiation nephritis, and when red blood-cells or cellular casts were found in the urine they were few in number. Oliguria was not seen except with congestive heart failure, although oliguria early in the disease may not have been recognized because the onset was gradual. In general the urine was that of chronic glomerulonephritis with renal failure. Again, anaemia is a much more important feature in acute radiation nephritis than in acute Bright's disease. Generalized oedema, however, is relatively uncommon in the former disease, and is associated with a stormy illness and grave prognosis. The clinical course of acute radiation nephritis is protracted, and complete recovery has not been observed. Considerable clinical and biochemical improvement may take place, but chronic nephritis with or without hypertension always persists after the acute phase.

2. *Hypertension in radiation nephritis.* Hypertension due to X-radiation of the kidneys may or may not be associated with renal failure. Hypertension arising after a latent period of eight months from the start of radiotherapy may be accompanied by the gross renal failure of acute radiation nephritis, or may be asymptomatic and may be discovered months or years later as benign hypertension. Again, there is evidence that neither hypertension nor albuminuria may appear until many months after radiotherapy, when hypertension in a most malignant form may arise, renal failure being secondary and terminal. Why these variations in reaction should be found in different patients is not clear, nor do we know why some men treated by the same method should appear to escape renal damage altogether. There is a suggestion, however, that a smaller total dosage of X-rays produces hypertension with relatively little renal failure.

3. *Anaemia in radiation nephritis.* It is not easy to account for the severe refractory anaemia of radiation nephritis. There was no clinical evidence of haemolysis, and studies of the serum-bilirubin and reticulocyte counts did not suggest haemolysis. It was also apparent that bone-marrow aplasia was not the cause, for the leucocyte and platelet counts were normal except in the very late stages, and sternal marrow examination in 16 patients showed an active marrow. Bone-marrow taken at autopsy from vertebrae within the field of immediate X-radiation was found to be active. Although anaemia due to marrow aplasia is a well recognized sequel to exposure to X-rays, under modern conditions aplastic anaemia is very rarely due to X-ray therapy, marrow aplasia being more frequent in workers exposed to X-rays or radium in small doses over long periods.

Abdominal X-ray baths must affect many structures of haemopoietic importance, notably the stomach and small intestine and the reticulo-endothelial tissues of the liver and spleen. Fractional gastric analysis was undertaken in 18 of this group of patients with radiation nephritis; seven had complete achlorhydria, which can be reasonably attributed to the effect of X-rays on the stomach mucosa. The intestinal mucosa is similarly sensitive to X-rays, but there has been no subsequent clinical indication of chronic insufficiency of the small intestine. Barium studies of the mucosal pattern and function of the small

bowel were made in two patients (Cases 1 and 8), and no significant abnormality was detected. Where autopsy was possible, the abdominal viscera were specially examined for any effect of deep X-ray therapy which may result in anaemia, but none was discovered. The spleen and a large volume of liver tissue must have been included in the radiotherapeutic fields in these patients. The tissues of the reticulo-endothelial system are sensitive to X-rays, advantage being taken of this sensitivity in the treatment of Hodgkin's disease and other reticuloses. In experiments on animals totally irradiated by X-rays the subsequent anaemia may be modified by protection of the spleen from irradiation (Cecil and Loeb, 1951). In the patients examined at autopsy there was no evidence of gross disease in the liver or spleen, other than some fibrosis of the interstitial tissue and capsule. The results of liver function tests in 17 patients were within normal limits, although, of course, the tests were made several months after the X-ray therapy had finished.

The anaemia of acute radiation nephritis is more severe than the associated increase in blood-urea would warrant if renal failure were the sole cause. (There is some correlation between the levels of haemoglobin and blood-urea in chronic renal failure; it was restated by Roscoe (1952) and Platt (1952), who indicated that each 50 mg. rise of urea per 100 ml. is accompanied by a fall of about 2 gm. per 100 ml. in haemoglobin.) It is probable, nevertheless, that the anaemia of acute radiation nephritis is due mainly to renal failure, for in its haematology and in its resistance to treatment it is identical with the anaemia seen in renal failure from other causes. Again, the onset of the anaemia in acute radiation nephritis appeared to synchronize with the onset of renal failure, and the anaemia improved along with renal function as the acute stage subsided. The view that renal failure is mainly responsible for the anaemia is supported by the rapid fall in the haemoglobin level in late malignant hypertension (Case 26).

Are the clinical syndromes of nephritis variants of one disease? It is noteworthy that a single known cause, scientifically measurable, can produce the typical syndromes of chronic glomerulonephritis, benign essential hypertension, and malignant hypertension. Moreover, in certain patients with generalized oedema the most acute radiation nephritis could easily be mistaken for acute Bright's disease. It is clear that, after X-irradiation of the whole of both kidneys, some patients show no evidence of renal damage, while others develop hypertension or one of the common nephritic syndromes. In addition to the common aetiology I would emphasize the underlying unity of the different clinical manifestations of radiation nephritis. It appears to be a basic disease which produces clinical syndromes in which the symptoms differ in degree and in tempo but not in nature. The renal tissue of different patients seems to vary in its reaction to X-radiation; the tissue reaction seems to determine not only the genesis of radiation nephritis but also the nature of the resulting clinical syndrome. It is probable that a similar condition holds good when the kidneys are exposed to noxious influences more common than X-radiation, such as streptococcal infections. Platt (1947) expressed the opinion that malignant and benign hypertension may be variants of one disease. The present study of

radiation nephritis suggests the further possibility that there is a basic relationship, closer than we have hitherto suspected, between many types of nephritis and renal hypertension.

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Case Reports

Acute Radiation Nephritis

Case 1. A man aged 35 years. Radiotherapy commenced on 17.11.49, 2,900 r being given during a period of 36 days. A preliminary chest radiograph and blood count were normal. Reaction to the X-ray treatment was seen in lung and pleura in radiographs taken in March and July 1950, but there were no symptoms.

August 1950: the initial complaints were dyspnoea on effort, ankle oedema, and pallor; considerable albuminuria was found. The blood-pressure was 185/90. The retinae were normal. A chest radiograph showed moderate cardiac enlargement. The red blood-cells were 2,040,000 per c.mm., haemoglobin 40 per cent., colour index 1.0, and white blood-cells 3,400 per c.mm. Microscopy of the urine showed a few red blood-cells and leucocytes; casts were not seen. The blood-urea was 98 mg. per 100 ml. Urea concentration test: specimen 1, 44 ml.; urea 1.65 per cent.; specimen 2, 53 ml.; urea 1.28 per cent.; specimen 3, 56 ml.; urea 1.65 per cent. The serum-albumin was 4.5 gm., and serum-globulin 2.4 gm. per 100 ml.

September 1950: blood transfusions raised the haemoglobin to 66 per cent. Four blood-urea estimations varied between 110 and 145 mg. per 100 ml.

October 1950: morning occipital headache occurred. There was no oedema, and the retinae were normal. The blood-pressure was 160/95. The urinary specific gravity was 1.010: albuminuria was considerable. There was some nocturia. The haemoglobin was 50 per cent., and blood-urea 97 mg. per 100 ml. Intravenous iron was given in large doses without benefit.

November 1950: the general condition was improved. The blood-pressure was 185/85. The blood-urea (five estimations) was between 83 and 120 mg. per 100 ml. The serum-bilirubin was 0.1 mg. per 100 ml. Coagulation and bleeding times were normal. The red blood-cells were 2,420,000 per c.mm., haemoglobin 46 per cent., colour index 0.96, and platelets 196,000 per c.mm.; reticulocytes were 0.8 per cent. Whole-blood transfusions restored the haemoglobin to 80 per cent.

January 1951: the general condition was still improving. The blood-pressure was 200/125. The haemoglobin was 58 per cent., and was restored to 74 per

cent. by whole-blood transfusion. The blood-urea was 80 mg., 89 mg., and 100 mg. per 100 ml.

April 1951: he complained of occasional headache, nausea, and vomiting. The retinae were normal, and the blood-pressure 175/95. The spleen was just palpable. Slight oedema of the shins was noticed. The red blood-cells were 2,300,000 per c.mm., haemoglobin 46 per cent., colour index 1·0, white blood-cells 7,700 per c.mm., platelets 170,000 per c.mm., and reticulocytes 0·7 per cent. Coagulation time, bleeding time, and prothrombin time were normal. The blood-urea was 112 mg. per 100 ml. Whole-blood transfusion restored the haemoglobin to 74 per cent.

July 1951: the patient had no complaints, but was pale and weak. The blood-pressure was 160/95. The specific gravity of the urine was 1,010; albumin was present. The red blood-cells were 2,560,000 per c.mm., haemoglobin 48 per cent., and colour index 0·94. The blood-urea was 63 mg. per 100 ml.

August 1951: Urea concentration test: specimen 1, 83 ml.; urea 1·6 per cent.; specimen 2, 66 ml.; urea 1·7 per cent.; specimen 3, 68 ml.; urea 2·0 per cent. The blood-urea was 118 mg. per 100 ml., serum inorganic phosphorus 3·6 mg. per 100 ml., and blood-creatinine 2·5 mg. per 100 ml. Urea clearance was 24 per cent. Further blood transfusion restored the haemoglobin to 78 per cent. and the red blood-cells to 4,000,000 per c.mm. The heart size was normal.

November 1951: the red blood-cells were 2,340,000 per c.mm., haemoglobin 45 per cent., and blood-urea 95 mg. per 100 ml. Urea concentration test: specimen 1, 62 ml.; urea 1·7 per cent.; specimen 2, 16 ml.; urea 3·4 per cent.; specimen 3, 25 ml.; urea 2·5 per cent. Urea clearance was 22 per cent. Further blood transfusions restored the haemoglobin to 78 per cent.

January 1952: the patient had no symptoms except occasional morning headaches. Albuminuria had persisted, and the urinary specific gravity was 1,010. The blood-pressure was 155/100, blood-urea 66 mg. per 100 ml., and urea clearance 24 per cent. The haemoglobin was 64 per cent.

Comment. After a latent period of eight months anaemia, hypertension, albuminuria, ankle oedema, and impaired renal function were noted. The anaemia has been severe and intractable, requiring 27 pints of whole blood by transfusion in 17 months. Blood-urea estimations, 28 in all, varied between 30 mg. and 145 mg. per 100 ml. Heart radiographs showed slight enlargement at eight months, moderate enlargement at nine months, and a return to normal size at 20 months. This is a case of acute radiation nephritis continuing into severe chronic nephritis.

Case 3. A man aged 29 years. Radiotherapy was started in November 1949, 3,000 r being the total dose during a period of 35 days. The patient returned to work in April 1950. Slight dyspnoea of effort was noticed in November 1950, and oedema of the face and ankles two weeks later. Frontal headache, anorexia, and vomiting occurred, but no urinary symptoms or haematuria.

27.12.50: the patient was pale, and had some cardiac enlargement. There was no oedema. The blood-pressure was 170/80. A small retinal haemorrhage was seen. The urinary specific gravity was 1,014, and the albumin content was 0·25 gm. to 2 gm. per litre. The red blood-cells were 1,610,000 per c.mm., haemoglobin 32 per cent., colour index 1·0, white blood-cells 7,700 (polymorphs 6,275, lymphocytes 1,347) per c.mm., and platelets 220,090 per c.mm. Serum-bilirubin was 0·7 mg. per 100 ml., total serum-proteins 5·8 gm. per 100 ml. (albumin 4·4 gm., globulin 1·4 gm.), and blood-cholesterol 200 mg. per 100 ml.

Thymol turbidity was 0·9 units. The blood-urea was 105 mg. per 100 ml. Urea concentration test: specimen 1, 52 ml.; urea 1·38 per cent.; specimen 2, 79 ml.; urea 1·35 per cent.; specimen 3, 67 ml.; urea 1·42 per cent. Urine microscopy revealed scanty granular and hyaline casts. A fractional test meal showed complete achlorhydria. A chest radiograph revealed moderate cardiac enlargement, and an intravenous pyelogram showed impaired concentration of the dye. Proteolysed liver was given for five weeks, 1½ ounces daily. On 7.1.51 three pints of whole blood were transfused, with clinical benefit, raising the haemoglobin to 50 per cent. Oedema of the face followed the transfusion.

24.1.51: there was no oedema. The blood-pressure was 170/90, and blood-urea 155 mg. per 100 ml. A further whole blood transfusion (four pints) was given.

7.2.51: the blood-pressure was 175/105. There was intermittent pyrexia to 102° F., attributed partly to anaemia, partly to respiratory-tract infection. The red blood-cells were 2,120,000 per c.mm., haemoglobin 40 per cent., colour index 0·95, and white blood-cells 7,200 per c.mm. The reticulocyte count was 0·2 per cent., and serum-bilirubin 0·7 mg. per 100 ml. Bleeding and coagulation times were normal.

19.2.51: clinically the patient was worse. The blood-urea was 195 mg. per 100 ml. The red blood-cells were 1,620,000 per c.mm., haemoglobin 32 per cent., and colour index 1·0. Four pints of whole blood were given by transfusion.

26.2.51: bright red blood was passed from the anus. The blood-pressure was 160/110. Hypertensive cardiac failure was present, with gallop rhythm, pulmonary oedema and haemoptysis, hiccup, and pericardial friction. The patient died on 2.3.51.

Autopsy report (Dr. Helen Russell). Considerable left pleural effusion was found, and some pericardial effusion with early fibrinous exudate. The lung bases were much congested. The wall of the left ventricle was hypertrophied, but the heart was not much enlarged. The coronary arteries were not diseased. Straw-coloured ascitic fluid was present; all the abdominal lymph-glands were inconspicuous. The spleen and pancreas were not diseased. In the stomach intense submucous congestion was present, but no free acid. The liver was congested. There was no sign of metastases. The kidney tissue was a symmetrical horseshoe organ with two ureters.

Histopathology. The pancreatic acini were irregular in size and shape. Pancreatic elements seemed reduced in quantity compared with islet tissue. One necrotic arteriole was found. The spleen was congested, and a little arteriolar degeneration was noted. The lymph-glands from the kidney hilum showed sinusoidal reaction and early fibrosis. In the suprarenal gland there was considerable lipoid in the middle zone of the cortex; no arteriolar lesions were noted. The suprarenal capsule was somewhat fibrotic. Marrow from the centre of the shaft of the femur showed no haemopoiesis. Marrow from the lumbar vertebrae was cellular, with excess of immature granulocytes and early red cells. Marrow from the sternum was very cellular, immature cells being in excess. *Kidney.* The capsule showed much fibrosis. Almost all the glomeruli were abnormal, with ill-defined hyalinization of the tufts and obliteration of capillary loops; very few were completely hyalinized. The tubules showed alternate areas of dilatation and atrophy. Endarteritis fibrosa of the intralobular vessels was present, varying in amount. No definite fibrinoid necrosis of arterioles was seen. Much intertubular fibrosis could be seen throughout. *Histological diagnosis.* Atypical nephropathy, probably ischaemic, but no marked hypertensive changes.

Comment. The first symptoms arose after a latent period of 12 months from the start of radiotherapy. Oedema of the face and ankles occurred early, but was not seen after admission. When first examined eight weeks after the onset, the patient was gravely ill with advanced anaemia and renal failure, and he failed to respond to repeated transfusions. He died of chronic uraemia and left ventricular failure within four months of the first symptom. Autopsy revealed a horseshoe kidney with capsular fibrosis; microscopically an atypical nephropathy was found, ischaemia being probable, but no marked hypertensive changes were evident. There was no gross lesion in the spleen, pancreas, stomach, or intestines. The marrow from the sternum and lumbar vertebrae was cellular, with excess of immature cells.

Case 4. A man aged 32 years. Radiotherapy was commenced in November 1949, the total dose being 3,000 r during a period of 37 days. A preceding blood count and chest radiograph were normal. Eight months after the commencement of radiotherapy oedema of the ankles and face occurred, and during six weeks the patient gained 14 pounds in weight. Occipital headache on waking would persist for an hour; dyspnoea on exertion began 10 days after the oedema. There were no urinary symptoms or haematuria, and no personal or family history of hypertension or renal disease.

19.9.50: examination showed considerable oedema of the legs, scrotum, and penis. The arteries and retinae were normal. Gross albuminuria was present. The blood-pressure was 165/85. The red blood-cells were 2,530,000 per c.mm., haemoglobin 50 per cent., colour index 1.0, white blood-cells 6,500 per c.mm., and platelets plentiful. Urine microscopy showed a few red corpuscles, leucocytes, epithelial cells, and granular casts. Urea concentration test: specimen 1, 70 ml.; urea 1.4 per cent.; specimen 2, 65 ml.; urea 1.5 per cent.; specimen 3, 110 ml.; urea 1.6 per cent. The blood-urea was 102 mg. per 100 ml.; the serum-proteins were normal. A chest radiograph showed considerable enlargement of the heart as compared with 14.12.49, with evidence of pleurisy at both bases. An intravenous pyelogram was normal except for poor concentration of the dye. An electrocardiogram was normal. In the sternal bone-marrow the normoblasts showed much variation in shape and size; there was evidence of failure of red-cell maturation.

18.10.50: bilateral pleural effusions, ascites, and oedema of the legs, back, and abdominal wall were now present. The blood-pressure was 170/90. The urine had a specific gravity of 1,008 to 1,012, and contained albumin 1 to 2 gm. per litre (Esbach); the daily output was about 50 ounces. The blood-urea was 73 mg. per 100 ml., serum-sodium 340 mg. per 100 ml., plasma-chlorides 610 mg. per 100 ml., and blood-cholesterol 206 mg. per 100 ml. The pleural fluid was clear and straw-coloured; a coagulum was present. Microscopy showed a few red corpuscles and endothelial cells. Intravenous injections of iron were commenced, the total dose being 3,200 mg. in 22 days.

10.11.50: the red blood-cells were 1,750,000 per c.mm., haemoglobin 36 per cent., colour index 1.02, and white blood-cells 5,500 per c.mm. The blood-pressure was 195/100. Retinal haemorrhages were present. The blood-urea was 140 mg. per 100 ml.

18.11.50: a purpuric eruption was found on the neck and chest. The haemoglobin was 44 per cent., and platelets 80,600 per c.mm. Bleeding and coagulation times were normal.

24.11.50: platelet count was 50,960 per c.mm., and haemoglobin 36 per cent. The Hess test was positive. Transfusion of packed red cells produced severe

dyspnoea, vomiting, sweating, and signs of pulmonary oedema, with an increase of blood-pressure to 220/140. Symptoms of left ventricular failure and chronic uraemia developed—vomiting, muscular twitchings, purpura, pericardial friction, drowsiness, and hiccup. Cortisone (25 mg. six hourly) was given, and two pints of whole blood were transfused.

4.12.50: blood-urea was 240 mg. per 100 ml. The patient died on 9.12.50.

Autopsy (Dr. Helen Russell). The abdomen contained a large quantity of greenish-yellow clear fluid. The intestines were dilated, with fluid contents. The liver was large, congested, and firm, with some perihepatitis on the anterior surface. The spleen was enlarged and congested. The pancreas was very firm. There appeared to be diffuse fibrosis of the upper aortic, perirenal, and peri-adrenal tissues; lymph-gland tissue was very scanty. Both kidneys were enlarged, and showed subacute cortical damage amounting almost to necrosis in places. The openings of the ureters into the bladder seemed small or contracted. The pelvic mucous membrane was thick, but no pyelitis was found, and the ureters were not obstructed, although a little periureteric fibrosis was noticed on both sides at the level of the bifurcation of the aorta. The capsules of the kidneys were a little adherent, and capsular fibrous tissue was denser than usual. The renal veins and arteries were not atheromatous. The suprarenal glands were small, and contained lipoid in the cortices; the medullary tissue was not diseased. The pericardium contained a large quantity of blood and clot. Fibrinous pericarditis was present. The heart-muscle appeared to be hypertrophied, especially on the left side.

Histopathology. The spleen contained much pigment within phagocytes, possibly a result of transfusion. The bases of both lungs showed a little increase of fibrous tissue and accumulations of 'heart failure' cells. The gastric mucosa was slightly atrophic. In the liver there was a slight increase of fibrous tissue. In the periureteric tissue, some distance below the kidney hilum, an irregular capillary disturbance and increased cellularity of the fat were seen. The mid-zone of the adrenal cortex showed cells distended with sudanophilic lipoids. *Kidneys*. Considerable fibrosis of the renal capsules was found. The glomeruli were almost all abnormal, tending to be collapsed or deformed, with ill-defined hyalinization of the tufts. A few showed patchy fibrinoid necrosis of the tuft. The tubules were mainly atrophic. Marked intertubular fibrosis was present. Focal fibrinoid necrosis was seen in intralobular arteries and arterioles. An occasional intralobular artery showed endarteritis fibrosa. Infarcts were present in the cortex. *Histological diagnosis*. The features suggest an atypical malignant nephrosclerosis.

Comment. The typical clinical picture of acute radiation nephritis commenced eight months after the start of radiotherapy. Generalized oedema was the first symptom, leading to an increase in weight of 14 pounds in six weeks. There was no haematuria. In the early stages the blood-pressure was only slightly raised, but anaemia and azotaemia were severe and defied treatment. A sharp reaction to blood transfusion occurred. Left ventricular failure, hypertension, haemorrhagic pericarditis, purpura, and signs of chronic uraemia led to death five months after symptoms began. At autopsy the kidneys were enlarged and the renal capsules thickened. Histologically the picture was that of an atypical malignant nephrosclerosis.

Case 6. A man aged 32 years. Radiotherapy was commenced in May 1948, 3,250 r being given during a period of 32 days. The patient's previous health

had been excellent. The blood count and coagulation time were normal; a chest radiograph showed a normal heart. There was no albuminuria. He was well until January 1949, when he complained of severe occipital headache and pleuritic pain. He was now very anaemic (haemoglobin 44 per cent.), and a chest radiograph showed considerable cardiac enlargement.

8.2.49: the red blood-cells were 1,600,000 per c.mm., haemoglobin 32 per cent., colour index 1.0, and white blood-cells 5,600 per c.mm. Blood transfusions raised the haemoglobin to 66 per cent.

15.3.49: headache occurred mainly over the vertex, but was often occipitonostral and associated with nausea, vomiting, photophobia, and blurring of vision. Dyspnoea and palpitation were occasional, but lassitude was constant. There was no oedema. Albuminuria was present. He appeared very anaemic, and purpuric spots were visible on the gums and skin. The heart was moderately enlarged; there was no valvular lesion; the blood-pressure was 205/125. The spleen was not palpable. Gross retinitis was found, seen as pararterial haemorrhages, white fluffy exudates, and oedema of both optic disks spreading on to the adjacent retina, but not of the 'choked disk' type. The cerebrospinal fluid was normal. Microscopy of the urine showed a few red cells and leucocytes. The blood-urea was 85 mg. per 100 ml. An intravenous pyelogram showed very poor concentration of the dye. Urea clearance was 25 per cent. Urea concentration test: specimen 1, 111 ml.; urea 0.91 per cent.; specimen 2, 114 ml.; urea 1.12 per cent.; specimen 3, 94 ml.; urea 1.25 per cent. The haemoglobin was 50 per cent.

25.4.49: the blood-pressure was 175/110. The red blood-cells were 2,860,000 per c.mm., haemoglobin 62 per cent., blood-urea 94 mg. per 100 ml., and urea clearance 18 per cent.

20.5.49: the blood-pressure was 175/120. The retinae were unchanged. The blood picture was unchanged in spite of intravenous iron. Headache and vomiting persisted. The blood-urea was 77 mg. per 100 ml.

8.6.49: the blood-pressure was 210/140, and blood-urea 55 mg. per 100 ml. The red blood-cells were 2,910,000 per c.mm., haemoglobin 61 per cent., and colour index 1.03. The urine had a specific gravity of 1.008, with albumin 1.75 gm. per litre (Esbach).

6.9.49: slow improvement had occurred. The blood-pressure was 195/125. There was no oedema. Both retinae showed clear-cut nodular exudates, and one pararterial haemorrhage was seen. In a chest radiograph the heart was diminished in size as compared with the film of January 1949. The red blood-cells were 3,130,000 per c.mm., haemoglobin 62 per cent., colour index 1.0, and leucocytes 6,400 per c.mm. The blood-urea was 36 mg. per 100 ml.

8.11.49: considerable improvement had occurred. The blood-pressure was 160/110. The retinal appearances were improving. Albuminuria was considerable. The haemoglobin was 66 per cent.

February 1950: the patient was back at work. The blood-pressure was 180/115. The retinae showed residual white nodular exudates only.

July 1950: The patient was very well; the blood-pressure was 165/115, and the retinae were clearing.

January 1951: albuminuria persisted. The blood-pressure was 170/110. The retinae were normal apart from small areas of pigmentation. The red blood-cells were 4,030,000 per c.mm., haemoglobin 76 per cent., colour index 0.95, and white blood-cells 6,600 per c.mm. The blood-urea was 25 mg. per 100 ml. on 3.1.51, and 52 mg. per 100 ml. on 31.1.51. There were no urinary casts. In an intravenous pyelogram both kidneys seemed small and irregular, and their function was depressed.

April 1951: the patient was able to play tennis. The blood-pressure was 150/105. The urinary specific gravity was 1,015; albuminuria was present. The blood-urea was 62 mg. per 100 ml.

July 1951: the blood-pressure was 150/100, and blood-urea 96 mg. per 100 ml. A chest radiograph showed the heart slightly larger than before radiotherapy, but distinctly smaller than in January 1949.

January 1952: there were no symptoms. The blood-pressure was 150/100. The urinary specific gravity was 1,012, and there was a trace of albumin. The red blood-cells were 3,890,000 per c.mm., and the haemoglobin 72 per cent. Bleeding and clotting times were normal. The urea clearance was 61 per cent. Urea concentration test: specimen 1, 85 ml.; urea 1·5 per cent.; specimen 2, 72 ml.; urea 1·7 per cent.; specimen 3, 92 ml.; urea 1·8 per cent. The blood-urea was 50 mg. per 100 ml.

Comment. After a latent period of seven months from the start of radiotherapy, typical signs and symptoms of severe renal failure arose, the urea clearance being 25 per cent. There was no oedema, oliguria, or haematuria. The symptoms were due mainly to high blood-pressure, and extensive retinopathy occurred. Thirty-six months after the onset of renal symptoms the patient is clinically well and lives a normal life; the retinae are normal, the blood-pressure is 150/100, and only a trace of albuminuria remains; urea clearance is 61 per cent.

Chronic Radiation Nephritis

Case 14. A man aged 38 years. Abdominal radiotherapy was begun in April 1949; the total dose was 3,000 r during a period of 33 days. The blood count was normal. Subsequently the patient was reported well when seen at three-month intervals until January 1951, 21 months after the start of radiotherapy. He then complained of lassitude and occasional occipital headache. There was no history of nocturia, haematuria, or oedema. Albuminuria was considerable; the urinary specific gravity was 1,010, and the blood-pressure 175/100. Clinical examination was otherwise negative. The blood-urea was 60 mg. per 100 ml. Microscopy of the urine showed a few red blood-cells and leucocytes, but no casts. Urea concentration test: specimen 1, 100 ml.; urea 1·35 per cent.; specimen 2, 50 ml.; urea 1·53 per cent.; specimen 3, 50 ml.; urea 1·06 per cent. The red blood-cells were 3,150,000 per c.mm., haemoglobin 64 per cent., and reticulocytes 0·3 per cent. Coagulation and bleeding times were normal, as were liver function tests, serum-proteins, blood-cholesterol, blood-chlorides, and serum-sodium. An intravenous pyelogram showed depression of renal function. The chest radiograph revealed moderate cardiac enlargement as compared with the heart size before radiotherapy. During January, February, and March 1951 the blood-urea was estimated eight times, the figures in mg. per 100 ml. being 60, 66, 95, 97, 52, 50, 92, 72. The urinary specific gravity remained between 1,008 and 1,012; albuminuria was persistent. Desiccated hog stomach was given by mouth, one ounce three times daily, for 21 days, without producing reticulocytosis or improvement in the anaemia. ACTH was then given six-hourly for 14 days, the total daily dose being 60 to 80 mg. The blood count subsequently showed red cells 2,750,000 per c.mm., haemoglobin 56 per cent., reticulocytes 1·1 per cent., and platelets 330,000 per c.mm. Transfusion of four pints of whole blood raised the haemoglobin to 84 per cent.

August 1951: in the preceding five months the blood-pressure had varied between 155/100 and 130/80, and the blood-urea between 68 mg. and 84 mg. per 100 ml. A blood count showed red cells 2,500,000 per c.mm., haemoglobin

50 per cent., and colour index 1.0. Transfusion of four pints of whole blood restored the haemoglobin to 78 per cent.

December 1951: the haemoglobin was now 54 per cent.; four pints of whole blood were transfused. The patient had remained fairly well and, although rather pale and lacking energy, had worked at a sedentary occupation. The blood-pressure was 160/90. Blood-urea estimations at intervals of a few weeks, taken while he was an out-patient, were, in mg. per 100 ml., 83, 60, 74, 82, 78, 54. The urea clearance was 26 per cent. Urea concentration test: specimen 1, 80 ml.; urea 1.9 per cent.; specimen 2, 76 ml.; urea 2.8 per cent.; specimen 3, 86 ml.; urea 1.7 per cent. A chest radiograph in October 1951 showed slight cardiac enlargement, mainly due to left ventricular hypertrophy.

Comment. Renal symptoms commenced 20 months after the start of radiotherapy. There was no acute stage. During 12 months' observation there were few symptoms; the blood-pressure, estimated 21 times, varied between 175/100 and 130/80; the blood-urea, estimated 21 times, varied between 50 and 100 mg. per 100 ml.; transfusion of four pints of blood was necessary on three occasions at intervals of four months. Renal function tests indicate no obvious deterioration. The anaemia was unresponsive to desiccated hog stomach, ACTH, iron, and vitamin C.

Benign Hypertension

Case 22. A man aged 35 years. Radiotherapy commenced in January 1947, 2,500 r being given during a period of 23 days. Blood count, urine examination, and heart size (chest radiograph) were previously normal. In June 1947 the patient complained of dyspnoea on exertion; a chest radiograph now showed a slight increase in the transverse diameter of the heart. The dyspnoea did not interfere with his work. In August 1947 the red blood-cells were 4,700,000 per c.mm., the haemoglobin was 92 per cent., and colour index 0.97. No symptoms other than nocturia had occurred since radiotherapy. There was no personal or family history of hypertension, and both parents are alive and well. On clinical examination in May 1951 the blood-pressure was 210/120. Cardiac hypertrophy was present. The retinae were normal. A trace of albumin was found in the urine. The blood-urea was 37 mg. per 100 ml., and the urea clearance 90 per cent. An intravenous pyelogram was normal. Urine microscopy showed a few granular casts. The red blood-cells were 4,510,000 per c.mm., the haemoglobin was 90 per cent., and colour index 1.0. Chest radiographs revealed left ventricular enlargement, and the electrocardiogram showed left axis deviation. Ten estimations of the blood-urea made between May 1951 and March 1952 gave upper and lower limits of 58 mg. and 28 mg. per 100 ml. Hypertension and slight albuminuria are persistent. The blood-pressure in March 1952 was 225/140.

Comment. This is a case of high blood-pressure in a young man with no personal or family history of hypertension, and apparently normal renal function. There is good evidence that the condition arose five years ago, six months after abdominal radiotherapy.

Case 23. A man aged 50 years. Radiotherapy began on 28.6.49, the total dose being 2,230 r during a period of 22 days. There was no personal or family history of hypertension. The blood-pressure was not recorded before radiotherapy, but the urine was normal, and the heart size was normal in a chest radiograph. Chest radiographs in August and November 1949 showed the heart

size unchanged; there was some lung reaction to the X-ray treatment. Chest radiographs showed the heart moderately enlarged in February 1950, and considerably enlarged in May and August 1950 (Plate 19, Fig. 2). There were no significant symptoms. Routine examination in March 1951 revealed considerable cardiac hypertrophy, radial arteriosclerosis, and normal retinae. The blood-pressure was 190/120. Albuminuria was present, the urine specific gravity was 1,020, and a few granular casts were found on microscopy. The blood-urea was 35 mg. per 100 ml.; urea concentration was normal; an intravenous pyelogram was normal. Serum sodium, chloride, proteins, and bilirubin were normal. The red blood-cells were 4,450,000 c.mm., haemoglobin 90 per cent., leucocytes 6,100 per c.mm., and platelets 230,000 per c.mm. Coagulation, bleeding, and prothrombin times were normal. An electrocardiogram showed left ventricular enlargement.

Course. There have been no symptoms. The urea clearance in December 1951 was 76 per cent. Eight recordings of blood-pressure have varied between 185/100 and 205/120. Nine estimations of the blood-urea have varied between 28 mg. and 52 mg. per 100 ml.

Comment. The hypertension has not been progressive during 12 months' observation. There has been no evidence of renal failure except an occasional slight rise in blood-urea. Chest radiographs suggest that the hypertension began about eight months after the start of radiotherapy.

Late Malignant Hypertension

Case 26. A man aged 35 years. In August 1949 abdominal X-ray baths were given, the total dose being 2,600 r during a period of 27 days. A preliminary chest radiograph was normal, as were those taken two months and six months after the start of radiotherapy. The patient remained well until February 1951, 18 months after the start of radiotherapy. He then complained of morning occipito-vertical headaches and some nocturia. He was rather pale, and the heart was slightly enlarged to the left; there was no oedema. The blood-pressure was 250/110. Gross albuminuria was present. Retinoscopy showed one flame-shaped retinal haemorrhage, but no papilloedema. The blood-urea was 38 mg. per 100 ml. The red blood-cells were 3,500,000 per c.mm., the haemoglobin was 72 per cent., and colour index 1.01; white corpuscles and platelets were normal. A few days later vomiting commenced, and the retinae showed haemorrhages, recent exudates, and early papilloedema. A few clearly demarcated exudates were also discovered.

12.3.51: the blood-urea was 45 mg. per 100 ml. An intravenous pyelogram was normal.

29.3.51: the red blood-cells were 3,320,000 per c.mm., haemoglobin 66 per cent., colour index 1.0, white blood-cells 9,300 per c.mm., platelets 130,000 per c.mm., and reticulocytes 0.3 per cent. The coagulation time was 14 minutes 25 seconds (normal for method 12 minutes); the bleeding time was 10 minutes 42 seconds (normal for method 7 minutes). Liver function tests, serum-proteins, sodium-potassium, blood-cholesterol, and whole-blood chlorides were normal.

6.4.51: the blood-pressure was 235/125; retinitis and papilloedema were severe, and purpura was found on the arms and trunk. The Hess test was positive. The prothrombin time was normal.

10.4.51: there were now signs of a localized vascular lesion in the pons. The blood-pressure was 250/125. The red blood-cells were 3,100,000 per c.mm., haemoglobin 64 per cent., colour index 1.02, white blood-cells 14,400 per c.mm.,

platelets 190,000 per c.mm., and reticulocytes 0·7 per cent. The blood-urea was 85 mg. per 100 ml.

13.4.51: the blood-pressure was 230/140. Headache and vomiting were severe, resisting treatment with intravenous hypertonic sucrose.

19.4.51: the red blood-cells were 2,050,000 per c.mm., haemoglobin 42 per cent., colour index 1·02, white blood-cells 10,400 per c.mm., platelets 180,000 per c.mm., and reticulocytes 2·4 per cent. The cerebrospinal fluid showed a resting pressure of 340 mm. There was no sign of spinal block. The lumbar cerebrospinal fluid was of a pale straw colour, and contained: cells, 178 per c.mm. (99 per cent. red blood-cells, 1 per cent. polymorphonuclear leucocytes); proteins, 70 mg. per ml.; globulin, slight opalescence (Pandy); urea, 75 mg. per 100 ml.

Albuminuria was considerable throughout. Urinary concentration was not impaired, and a specific gravity of 1,020 was found within 10 days of death. In chest radiographs taken on 11.8.49, 17.10.49, and 6.2.50, the heart size was normal. In a radiograph of 29.3.51 the heart showed slight enlargement. The patient died on 21.4.51. Autopsy was refused.

Comment. For 18 months after the start of radiotherapy this man was apparently well. Symptoms and signs of severe malignant hypertension then arose, and death followed within seven weeks. At the onset of symptoms the blood-urea was 38 mg. per 100 ml., and haemoglobin 72 per cent.; within six weeks normochromic anaemia developed (haemoglobin 42 per cent.), and the blood-urea increased to 85 mg. per 100 ml. Chest radiographs showed only slight cardiac enlargement three weeks before death.

Case 27. A man aged 44 years. Abdominal radiotherapy was started in November 1948, 3,000 r being given during a period of 25 days. Apart from slight dyspnoea of effort, the patient remained well and at work until November 1950, when he complained of dyspnoea and swelling of the feet. The heart was then enlarged, the blood-pressure was 225/100, and moderate oedema of the feet was found. Gross retinitis was present, appearing as bilateral papilloedema, haemorrhages, and white exudates. Albuminuria (2 to 3·5 gm. per litre) was noted, the urine having a low specific gravity. The liver was much enlarged, but the spleen was not palpable. Signs of basal oedema were present in the lungs. The red blood-cells were 1,980,000 per c.mm., haemoglobin 39 per cent., colour index 1·0, platelets 118,800 c.mm., white blood-cells 11,500 per c.mm. (polymorphs 8,682, lymphocytes 2,127), and reticulocytes 6·9 per cent. The blood-urea was 154 mg. per 100 ml., the whole-blood chlorides 550 mg. per 100 ml., serum-sodium 340 mg. per 100 ml., and blood-cholesterol 170 mg. per 100 ml. The total serum-proteins were 6·1 per cent. (albumin 3·5 per cent., globulin 2·6 per cent.; albumin/globulin ratio 1·35). Liver function tests were normal. An electrocardiogram was normal except for some flattening of the T waves in the standard leads. Two pints of whole blood were transfused; skin purpura developed later. Rapid progress of congestive heart failure led to death on 18.12.50, seven days after admission to hospital. The size of the heart was the same in chest radiographs of 24.11.48, 12.4.49, and 9.8.49. A radiograph of 12.12.50 showed transverse enlargement of the heart.

Autopsy (Dr. Helen Russell). A quantity of fairly clear fluid was found in both pleural cavities; the lungs were oedematous. The heart was relatively large (weight 625 gm.) but no disease of the arteries or valves was found. There was some excess of pericardial fluid. The spleen was unusually small, and showed

old perisplenitis. There was no free acid in the stomach. The small intestine was not diseased, except for numerous adhesions between loops. The transverse colon was adherent to the small intestine. The liver showed an increase of capsular fibrous tissue, and was rather firm on section. The kidneys were of normal size and not unusually bound down; their capsules were not densely adherent; the renal pelves were not diseased. The ureters were normal, and nothing unusual was seen in the bladder or prostate. The adrenals were rather small, and cortical lipoid was conspicuous.

Histology. In the pancreas some diffuse fibrosis was noted. The endothelial cells of the liver sinusoids were conspicuous, and the intercellular reticulin was slightly increased. In the spleen the medullary tissue was laden with pigment, possibly owing to transfusion, and the follicles were conspicuous. The mid-zone of the suprarenal cortex was laden with lipoid; the inner zone was congested. The adrenal medulla appeared to be normal. The thyroid and pituitary were normal. The heart showed slight coronary atheroma, but the muscle was not diseased. Bone-marrow from the femoral shaft was completely aplastic. The lumbar vertebrae contained only patches of cellular marrow, but these showed erythropoiesis and granulopoiesis. Occasional normoblasts were minute. The sternal marrow was very cellular; some cells of the erythrocyte series were abnormally small, and there was a shift to the left in the granulocytes. *Kidney.* The great majority of the glomeruli were abnormal; most were somewhat shrunken, and showed partial hyaline obliteration of capillary loops. A few showed haemorrhagic infarction; a crescent was occasionally seen, and a small number of glomeruli were completely hyalinized. The tubules were mainly small; many were atrophic and embedded in fibrous tissue. Hyaline arteriosclerosis and endarteritis fibrosa of intralobular arteries was noted, and also fibrinoid necrosis of arterioles. Some increase in fibrous tissue was present in the renal capsule. *Histological diagnosis:* severe hypertensive nephrosclerosis.

Comment. For two years after the start of radiotherapy this man continued strenuous work. Severe hypertension, anaemia, and renal failure were then found, and he died within six weeks of the onset of symptoms. Autopsy showed kidneys of normal size, and renal capsules slightly thickened but not unduly adherent. The heart was enlarged; some perihepatitis, perisplenitis, and adhesion between intestinal loops were noticed. Bone-marrow in the sternum and lumbar vertebrae was cellular, but some excess of early forms of red cells was present. Microscopically, the kidney showed severe hypertensive nephrosclerosis.

Summary

1. Nephritis may result when all the renal tissue is included within a therapeutic field of deep X-rays. Twenty-seven patients with radiation nephritis were studied clinically, and a preliminary comment is made on autopsy findings in four of the seven who died.
2. The syndromes arising are described as acute and chronic radiation nephritis, benign hypertension, and late malignant hypertension.
3. Thirteen cases of acute radiation nephritis (five fatal) were studied in detail. From the start of radiotherapy there was an asymptomatic latent period of six to 12 months (usually eight months). The main clinical features were oedema, urinary changes, hypertension, anaemia, cardiac enlargement, head-

ache, retinitis, dyspnoea, nausea and vomiting, lassitude, nocturia, and drenching sweats. Oedema was found in the majority of patients. In a minority generalized oedema, shown by a rapid increase in weight, was an early symptom. Pleural effusions and ascites occurred in the fatal cases only. The urinary changes included persistent albuminuria, low urinary specific gravity, and the presence of urinary casts or a few red blood-corpuscles. Gross haematuria did not occur. Hypertension usually developed early, but was sometimes delayed. The blood-pressure tended to fall to normal if the patient survived for six months. Severe and refractory anaemia was an early and constant feature. The anaemia was normochromic and normocytic, and not due to marrow aplasia or haemolysis. It is regarded as an effect of renal failure, although its severity is greater than would be expected from renal failure alone. Cardiac enlargement occurred at an early stage in all cases. Renal function, usually impaired at first, improved gradually in the patients who survived. There was a relationship between the sustained level of the blood-urea and the progress of the anaemia; as renal function improved the need for blood transfusion became less. A bad prognosis was indicated by severe oedema, or by a blood-urea over 100 mg. per 100 ml. at some time during the first three months of the illness. Factors of little prognostic value were the latent period, the age of the patient, the blood-pressure in the early stages, and renal function tests during the first five months. Patients surviving for six months from the onset showed great improvement, but all had residual chronic nephritis. Treatment was symptomatic. Rest in bed and repeated blood transfusions kept certain patients alive until the acute stage of the disease had subsided. Death was due to left ventricular failure, congestive heart failure, hypertensive encephalopathy, and uraemia.

4. Chronic radiation nephritis may follow acute radiation nephritis, or may develop insidiously. It has the usual clinical and biochemical features of chronic glomerulonephritis. The syndrome of Type 2 nephritis (Ellis) was not observed to follow renal X-radiation.

5. A condition resembling benign essential hypertension occurred in four cases. It was asymptomatic, but studies of serial chest radiographs suggest that the hypertension began about eight months after the start of radiotherapy. One such case is of five years' duration.

6. Malignant hypertension developed long after the radiotherapy, without significant preceding symptoms. Two cases are described which occurred 18 and 24 months after radiotherapy; both patients died within seven weeks of the onset of symptoms.

7. Periodic chest radiographs show changes in the size of the heart which suggest that acute radiation nephritis and 'benign hypertension' began about eight months after the radiotherapy. Cases of chronic radiation nephritis and late malignant hypertension showed only left ventricular enlargement, which developed gradually and late.

8. Autopsy in four cases showed a layer of fibrous tissue between the peritoneum and kidneys. The kidney capsules were thickened, but not unduly adherent. The kidneys were usually of normal size. Constrictive perinephritis

is a possible but unlikely explanation of the hypertension. The histological changes in the kidneys are unique. Characteristic features are widespread fibrosis between atrophic tubules, damage to almost all the glomeruli, and fibrinoid necrotic lesions of arterioles.

9. Radiation nephritis is one disease, in spite of its various clinical manifestations. Its features suggest that there is possibly a common basis for the various types of nephritis and renal hypertension.

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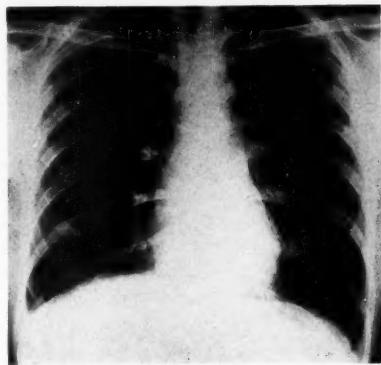


FIG. 1a. Case 6. Before radiotherapy

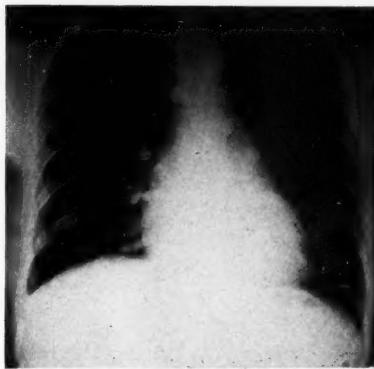


FIG. 1b. Case 6. Moderate generalized cardiac enlargement eight months after the start of radiotherapy

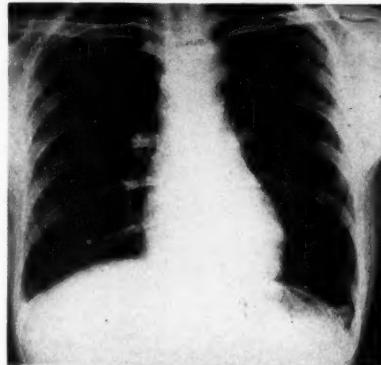


FIG. 1c. Case 6. Reduction in heart size 16 months after the start of radiotherapy.
Aortic arch enlarged

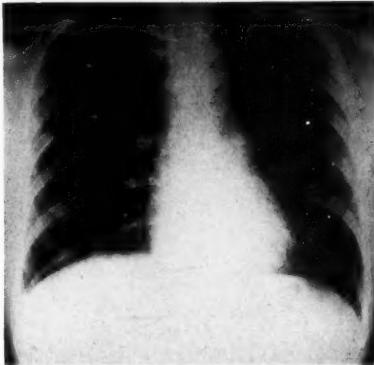


FIG. 1d. Case 6. Heart size almost normal 38 months after the start of radiotherapy

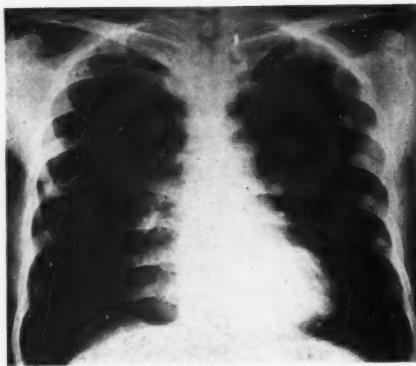


FIG. 2a. Case 23. Before radiotherapy

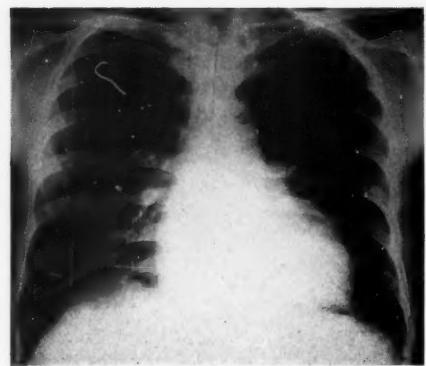


FIG. 2b. Case 23. Moderate generalized cardiac enlargement eight months after the start of radiotherapy

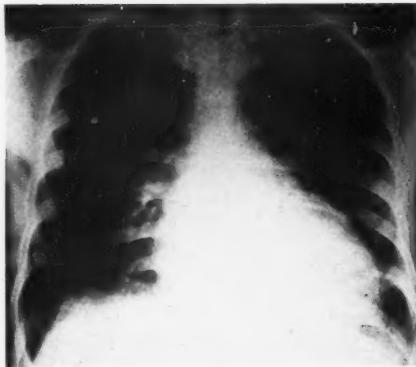


FIG. 2c. Case 23. Gross cardiac enlargement 11 months after the start of radiotherapy

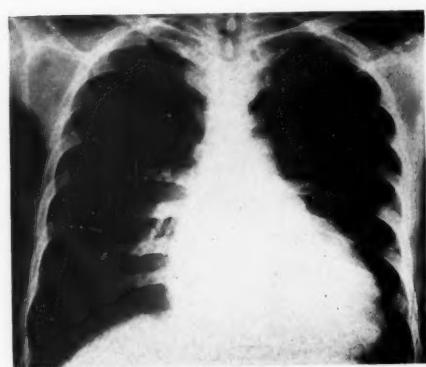


FIG. 2d. Case 23. The heart still grossly enlarged 21 months after the start of radiotherapy

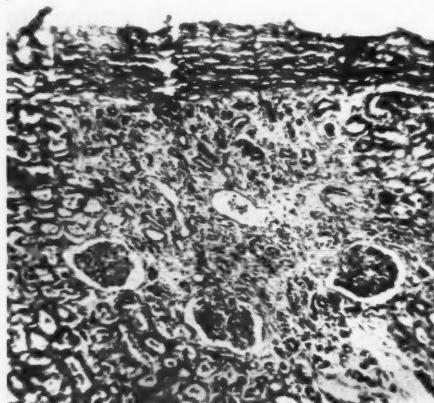


FIG. 3. Case 3. Kidney. Low-power view showing fibrosis of the capsule, with a subjacent area of ischaemic fibrosis in which lie atrophic tubules (haematoxylin and eosin, $\times 65$)

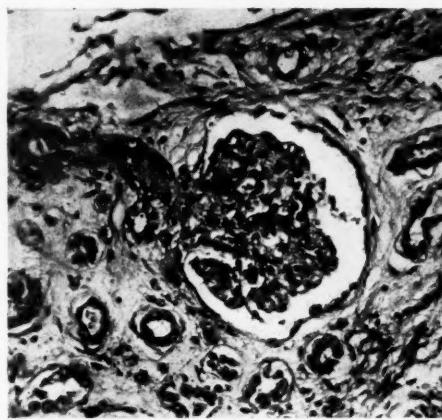


FIG. 4. Case 3. Fibrinoid necrosis of an afferent arteriole is well shown. The glomerulus shows some ischaemic collapse. The intertubular fibrosis is pronounced; the tubules are atrophied (haematoxylin and eosin, $\times 116$)

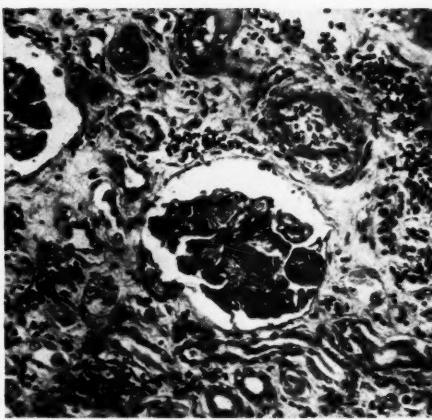


FIG. 5. Case 4. The glomeruli are deformed and show hyaline obliteration of capillary loops. Fibrosis and round-cell infiltration of the interstitial tissue are present. Arterioles show marked hyaline thickening of their walls (haematoxylin and eosin, $\times 116$)

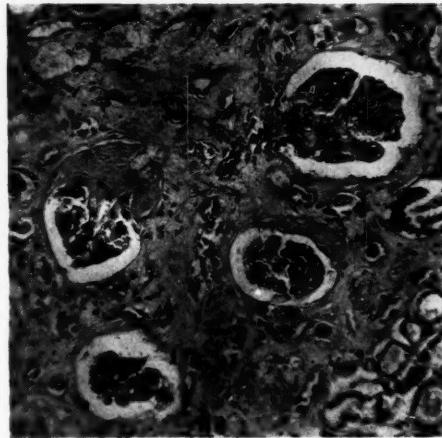


FIG. 6. Case 5. The glomeruli show varying degrees of hyalinization and ischaemic collapse. Fibrosis of the interstitial tissue is pronounced, and tubules are grossly atrophic (haematoxylin and eosin, $\times 116$)

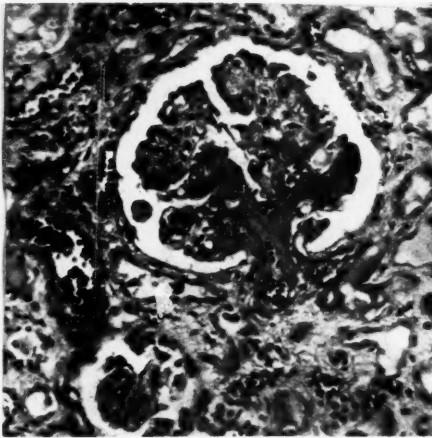
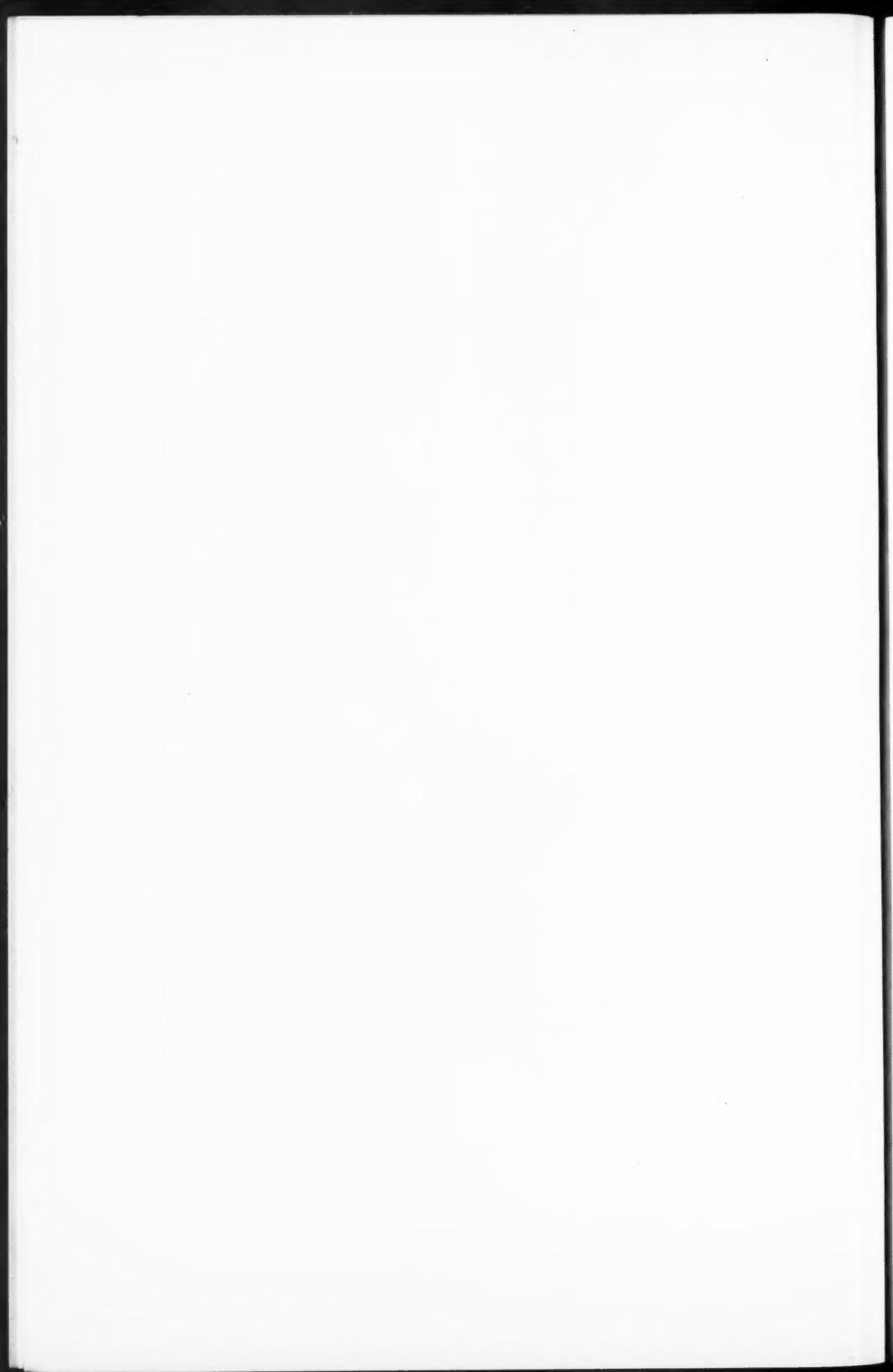


FIG. 7. Case 27. The glomerulus shows obliteration of capillary loops and fibrinoid necrosis in its lower central portion. Surrounding tubules are lined by atrophic epithelium, and intertubular fibrosis is marked (haematoxylin and eosin, $\times 116$)

Figs. 3-7 are reproduced by courtesy of the *British Journal of Radiology*



PAPILLOEDEMA AND FITS IN HYPOPARATHYROIDISM¹

With a Report of Three Cases

By D. KERR GRANT

(From the Clinical Research Unit, Royal Prince Alfred Hospital, Sydney)

THE occurrence of papilloedema in certain patients with hypoparathyroidism was apparently first described nearly 50 years ago (Luettwig, 1903, quoted by Albrecht, 1923). The condition, although rare, is not without clinical importance because incorrect diagnosis may lead to dangerous and profitless investigations, while the patient is deprived of specific medical treatment which alone can provide a proper remission. This was the early course of events in the cases to be reported in the present paper, for, as on previously recorded occasions (Barr, MacBryde, and Sanders, 1938; Hurxthal, 1942; Sutphin, Albright, and McCune, 1943; Leonard, 1946; Levy, 1947; Berezin and Stein, 1948), the presence of a space-occupying lesion of the cranium was at first suspected, and the tetany was regarded as coincidental. As in other rare disorders, it is difficult to be sure that the rarity of the condition is not more apparent than real. In chronic parathyroid tetany, however, lenticular cataract is such a frequent complication that expert ophthalmological examination is usual. In these circumstances it is improbable that papilloedema is often overlooked unless it is of short duration. I have been able to find only 25 cases previously reported in the medical literature, but have made no search of publications in languages other than English, with the exception of the article by Albrecht (1923), the earliest source consulted. He reviewed the syndrome, collecting 10 previously described cases from the German and Italian literature (only two of which are mentioned in any detail), and reporting one case observed by himself. In the English-speaking countries it was not until 1934 that Shelling and Goodman discovered 'bilateral choked disks' as an incidental finding in a patient with chronic tetany, and related this feature to concomitant epilepsy. Barr, MacBryde, and Sanders reported two cases in 1938. I have assumed that the same two patients were referred to by C. M. MacBryde in the discussion which followed the paper of Eaton and Haines (1939). Hurxthal (1942) reported a case occurring after operation, and in the following year Sutphin, Albright, and McCune (1943) described the occurrence of papilloedema in one of three siblings suffering from idiopathic hypoparathyroidism. Another patient of theirs also had a raised cerebrospinal fluid pressure (220 mm. of water). This, however, was apparently an isolated reading, and as there is no record of an examination of the fundus oculi I have not included the case in the present series. Lillie (1945) demonstrated

¹ Received September 11, 1952.

a patient with optic neuritis and cataracts developing after thyroidectomy, and in the same year Evans and Elliott (1945) reported a similar condition in a patient with primary parathyroprivia. In the ensuing year Leonard (1946) and Mortell (1946) each presented a further example of the condition. Additional cases described by Levy (1947), Berezin and Stein (1948), Lyle (1948), Collins-Williams (1950), and Steinberg and Waldron (1952), with those reported below, bring the total number recorded to 28.

The origin of the hypoparathyroidism is known in 22 of these cases. In 11 it was idiopathic, and in the remainder it occurred after thyroidectomy, five patients having undergone operation for thyrotoxicosis, and six for non-toxic goitre, so far as can be ascertained from the records. No correlation can be observed between the apparent duration of the tetany and recognition of papilloedema, the intervals varying from about three weeks (Collins-Williams, 1950) to 14 years (Barr, MacBryde, and Sanders, 1938), with an average of approximately four years. The age incidence ranged from six years (Collins-Williams, 1950) to 59 years (Steinberg and Waldron, 1952), and female patients were affected more commonly than male (13 cases to five); in the remainder the sex is not stated. Tuberculosis was associated in one case (von Frankl-Hochwardt, 1907, quoted by Albrecht, 1923), and Addison's disease in another (Leonard, 1946). Myxoedema does not appear to have been present in a single case. Other features of chronic tetany, such as psychotic changes, epileptiform convulsions, and electroencephalographic abnormalities occurring with papilloedema, may strongly suggest a provisional diagnosis of cerebral tumour. In this event a period of adequate therapy with complete symptomatic and biochemical control of the tetany should be given a trial (as in the second patient reported by Barr, MacBryde, and Sanders, 1938), before such measures as ventriculography and craniotomy are employed. The importance of the possibility that raised intracranial tension may develop in an improperly managed case of chronic hypocalcaemic tetany, with the chance of a fatal issue, does not need emphasis. Treatment of the tetany should be prompt and efficient as soon as such a condition is suspected, for there is a risk of permanent cerebral damage if the raised tension be prolonged (Barr, MacBryde, and Sanders, 1938; Leonard, 1946; Mortell, 1946). It seems likely, in such cases of hypoparathyroidism, that papilloedema and raised intracranial tension, resulting from cerebral oedema, are closely related to the disturbances of cerebral function mentioned above. These features of the condition will be discussed, and a common mechanism tentatively suggested which may explain them. Their exact physico-chemical pathogenesis remains unknown. In the three patients reported below the electroencephalographic technique of Gastaut (1950) was used in an attempt to classify the epileptic seizures.

Case 1. Mrs. F. G. H., at the age of 33 years, developed tetany three days after total thyroidectomy for non-toxic goitre. Treatment of the tetany was inadequate, and in addition to cramps and paraesthesiae in her limbs she developed headaches and mental unrest. She came of neuropathic stock, and even before the operation had shown symptoms of mild psychic disturbance.

In June 1948, six months after operation, she was found to have bilateral papilloedema, with normal visual fields and acuity. The cerebrospinal fluid pressure was 245 mm., and an X-ray of the cranium was normal. The report on an electroencephalogram was as follows: 'Resting record: the dominant frequency is an 8-c.p.s. alpha rhythm of very high voltage, nearly $100\mu\text{v}$. The frontal alpha rhythm is also of higher voltage than usual. Theta activity is very prominent, especially in the frontal regions, where it occurs in long runs of 7-c.p.s. waves. Paroxysmal episodes of high-voltage 7-c.p.s. waves with some positive down-peaks also occur in all leads, of highest voltage in the frontal region. On hyperventilation there is a marked increase in the voltage of the alpha rhythm and the amount of theta rhythm. Interpretation: this is a grossly abnormal record, showing a generalized dysrhythmia of the type commonly seen in the psychomotor type of epilepsy.' There were no further localizing signs, and the provisional diagnosis of frontal-lobe tumour was considered. Ventriculography, however, revealed a small, but otherwise normal, ventricular system, and the alternative diagnosis of cerebral thrombophlebitis was made. The cerebrospinal fluid pressure remained raised, with readings up to 460 mm., and the papilloedema was thought to be increasing. In November 1948 her vision became blurred, and she suffered from vomiting. A further electroencephalogram was performed, and showed a dysrhythmia similar to the previous tracing, with marked sensitivity to overbreathing. Right subtemporal decompression was performed. This did little to improve her symptoms, and the cerebrospinal fluid pressure continued at levels of 240 to 330 mm. Papilloedema was still present. In the last week of April 1949 she had five generalized epileptiform seizures. There was no family history of epilepsy, and she had never before had a fit. Electroencephalograms were repeated on two occasions, and both showed 'a general and focal slow-wave dysrhythmia. In each there is persistent focal delta activity of high voltage from placement 10, one cm. above the pinna, and other transient delta foci are seen, especially in the earlier recording, in the left post-central region and right frontal. The first record was much more active than the second. Both show bilaterally synchronous runs of 5-c.p.s. waves in the frontal records. At first these records give the impression that they are those from a severe epilepsy because of their rhythmic, paroxysmal high-voltage discharges. However, it is considered that the persistent focus from placement 10 represents the surface extension of an infiltrating tumour (? glioblastoma multiforme) which is also involving the thalamus.' The cerebrospinal fluid pressure was still high, and the papilloedema remained unchanged. There were no focal neurological signs. Ventriculography was repeated. Again no localized lesion could be demonstrated. It was considered that the persistent right temporal focus in the electroencephalograms must be related to the operative interference.

In May 1949 the possibility that the disorders of her central nervous system could all be attributed to tetany was first discussed. Adequate and sustained treatment of her tetany was for the first time begun with dihydrotachysterol and calcium by mouth. After one month's treatment the cerebrospinal fluid pressure had fallen to 170 mm., and her symptoms had so improved that she was discharged from hospital. By September it was noticed that her papilloedema had subsided. In December 1949, in view of the expense, calciferol was substituted for dihydrotachysterol.

In March 1950 she was readmitted to hospital for further investigation. During the preceding nine months her general condition had improved, but she still complained of headache and poor memory. There was bilateral secondary optic atrophy, but visual acuity was normal. She was given a diet containing

a fixed amount of calcium, with added calcium and calciferol by mouth (Table I). The Sulkowitch test showed a faint cloud in 24-hour specimens of urine. X-rays of the cranium and long bones revealed no abnormal intracranial calcification, no osteoporosis, and no excessive bone density. A further electroencephalogram showed 'a normal tracing except for the persistent focus in the right temporal region'. Lumbar puncture was performed, producing a clear fluid at a pressure of 155 mm. On May 1, 1950, the patient was deprived of added calcium and calciferol, while the diet remained the same in other respects. Troussseau's sign

TABLE I
Case 1

Period	Diet		Treatment (daily)	Date	Serum chemistry		
	Calcium (gm.)	Phosphorus (gm.)			Ca (mg./100 ml.)	P (mg./100 ml.)	Total protein (gm./100 ml.)
Mar.-May 1950	1.2	..	Calcium 0.3 gm. Calciferol 150,000 u.	10.4.50 24.4.50	10.1 12.3	2.9 4.1	7.9 8.0
			None	15.5.50 22.5.50 3.7.50	9.3 8.8 7.3	4.8 4.5 4.3	..
July-Sept. 1950	1.2	..	Calcium 0.3 gm. Calciferol 75,000 u. Parathormone 10 u. 24.7.50-2.8.50 and 14.8.50-2.9.50	17.7.50 24.7.50 7.8.50 28.8.50 4.9.50	7.7 8.0 8.5 8.1 9.5	4.8 4.6 3.4 4.1 4.1	..
			Calcium 2.5 gm. Calciferol 150,000 u.	18.9.50 5.12.50 6.3.51 3.7.51	10.0 10.4 8.1 11.7	4.5 5.8 5.8 5.9	..
			Calcium 2.5 gm. Calciferol (from 18.7.51) 180,000 u.; (from 8.8.51) 200,000 u.	11.7.51 1.8.51 8.8.51 29.8.51	8.9 12.8 14.2 10.8	5.3 5.5 4.6 5.3	..
Aug.-Oct. 1951	0.3	0.6	Calcium 2.5 gm. Calciferol 150,000 u.	19.9.51 26.9.51 4.10.51 17.10.51	10.2 12.1 12.1 12.1	4.5 4.8 4.8
			(In addition) colloidal aluminium hydroxide suspension 30 ml.	14.11.51 21.11.51	11.3 11.3	5.7 3.5	..
From 17.10.51							

became positive after a fortnight, and after three weeks the patient had a spontaneous attack of aching pain in her arms and legs, and became very confused and disorientated. On June 19 the cerebrospinal fluid pressure was 150 mm. The serum-calcium continued to fall slowly, while the serum-phosphorus was almost unchanged. The Sulkowitch test showed a faint cloud. Troussseau's sign became more strongly positive, although Chvostek's sign remained negative. The patient frequently complained of aching and stiffness in the limbs. The fundi still showed atrophy at the nerve-head, but no papilloedema. Nine weeks after deprivation of added calcium and calciferol the patient had a generalized major epileptiform seizure with superimposed carpopedal spasm. The serum-calcium was 8.1 mg. per 100 ml., while other serum-electrolytes in the same specimen (Na, K, Cl, CO₂, P) were normal. The patient recovered from her fit after about three minutes, and she had no more. Next day an electroencephalogram showed 'a reversion in the direction of the earliest records, with a general slow-wave dysrhythmia. There is marked deterioration as compared with the almost normal record in April 1950.' She was at once treated again with calcium lactate and calciferol (Table I). After two weeks Troussseau's sign had become negative, and the patient felt well, being free from

stiffness and pain in the limbs. Examination of the eyes by the slit-lamp on July 24 revealed a few fine peripheral striae in both lenses. The serum-calcium rose slowly, and the precipitate in the Sulkowitch tests gradually increased until a moderate cloud was seen. In order to attempt acceleration of her recovery, intramuscular injections of parathyroid hormone were given, and the dosage of calcium and calciferol was increased. On September 20, 1950 a further electroencephalogram showed an abnormal tracing, although there was some improvement since the previous record. On October 13, 1950 she was discharged from hospital to attend as an out-patient. In view of the unpleasant taste of calcium lactate, and its apparent tendency to induce diarrhoea, calcium gluconate had been substituted for the past month, and she was told to continue taking it, and also calciferol. The patient now felt in fair health, although she still had occasional headaches and found difficulty in mental concentration.

Her clinical condition continued much the same in the succeeding months. There was no frank or latent tetany, and no further epileptiform attacks. Her fundi showed no change. She still complained of occasional headaches, poor memory, and feelings of vagueness. On March 29, 1951 an electroencephalogram was still abnormal, with accentuation of abnormalities on overbreathing, and a repetition three months later showed no improvement. Her dose of calciferol was increased slightly, and after a further month a dietary restriction of phosphorus was made. Six weeks later, on October 17, colloidal aluminium hydroxide was added to the treatment. On November 21, 1951 electroencephalography was performed again. The resting record was now substantially normal. Her 'myoclonic threshold' with combined leptazol-flicker stimulation was estimated. At a dose corresponding to 11.7 mg. of leptazol per kg. body-weight a myoclonic response was obtained, followed immediately by a typical grand mal seizure. 1.5 gm. of troxidone was injected intravenously, and the patient recovered without further incident; she had no recollection of her fit. She continues to complain of frontal and temporal headache, and her memory is still rather vague, but otherwise she is well.

Case 2. Mrs. G. H. had a subtotal thyroidectomy performed for thyrotoxicosis in October 1941, when aged 20 years. Three days afterwards she developed tetany, which was treated, but without adequate relief. Two months after operation she had an epileptiform fit, in which she lost consciousness and bit her tongue. There was a history of convulsions in infancy, but no family history of epilepsy. She had further fits in the ensuing weeks, and in February 1942, four months after the operation, began to have periods of semi-coma lasting about four days. Cerebral tumour was suspected. Lumbar puncture was done, and a skull X-ray was taken, but we have no record of the results of these examinations, nor of the appearance of the fundus oculi. A neuro-surgical opinion apparently did not support the diagnosis of cerebral tumour. Fits continued for the next nine months, and appeared to be associated with her menstrual periods, occurring on about the third or fourth day of the period. Her tetany also appeared worse during menstruation. Some relief was afforded by intramuscular or intravenous injections of calcium gluconate at these times. She was also taking irregular amounts of calcium by mouth. Her fits appeared to occur independently of the severity of the tetany. She has never had any anti-convulsant therapy.

In December 1942 she married, and in August 1943 gave birth to a normal child. During her pregnancy she was apparently very well, being free both from tetany and from fits. She had breast-fed her child satisfactorily for seven months when tetany recurred. Treatment was resumed, but after a few

months attacks of tetany were still occurring at very frequent intervals. She was again taken into hospital, where she was treated with a diet containing large amounts of milk and butter, and in addition was given intramuscular injections of parathyroid extract. Relief was slight and temporary; after three weeks she was discharged, and continued taking small doses of calcium gluconate and calciferol. These were inadequate for the complete control of symptoms. Early in 1945 she again became pregnant, and for several months was free of tetany. By August she had begun to suffer from spasms in her hands and feet, and was advised to increase the dose of calciferol and to take extra milk. (She continued to take large amounts of milk in her diet until she came under treatment in the Clinical Research Unit.) In October 1945 she was delivered of a normal female child. She had breast-fed this infant for seven months when she had an epileptiform seizure, the first since her marriage. During the ensuing months she developed morning headaches, and had difficulty in hearing. Her speech became confused, and she had difficulty in following the train of events. She was readmitted to hospital in August 1946, and was found to have bilateral papilloedema, more severe on the right side. She was again treated with calcium, and for the following 15 months was receiving two or three injections each week as an out-patient. During the latter part of this period she began, for the first time, to notice deterioration of her vision. In November 1947 she became pregnant for a third time, and ceased to attend for treatment. In July 1948 she was delivered of healthy twins. She had been relatively free from tetany, as in her previous pregnancies; but immediately after delivery she suffered a recurrence. She did not breast-feed the twins. In none of her pregnancies had she been subject to vomiting. For the next year or so her tetany continued, with exacerbations associated with menstruation, and she was again given calcium injections. Her vision also became worse. Bilateral cataracts had been diagnosed, and a left intracapsular extraction was performed in January 1950. The right eye was similarly dealt with in June. Vision became 6/6 in both eyes with correction, and both fundi were normal. One month after the second operation she had pneumonia. There was a recurrence of the epileptiform fits, and she was readmitted to hospital, where treatment with calcium relieved her symptoms. During one of her fits she had a vitreous haemorrhage on the left side, and she is still blind in that eye. She had intermittent tetany for a further 12 months, and in July 1951 she again had a generalized seizure, after which she was stuporose for four days. She was referred to the Clinical Research Unit in September 1951 for investigation and stabilization of treatment.

On admission her main complaint was of poor memory and forgetfulness. She was also emotionally unstable, being unduly excitable and irritable. There was no manifest tetany. On examination her right fundus oculi was normal, but the left could not be seen owing to the old haemorrhage. The nails of all the fingers and toes showed brownish transverse ridging. Both Chvostek's sign and Troussseau's sign were positive. Apart from dental caries of four years' duration, other findings were substantially normal. X-rays of the skull revealed no abnormal intracranial calcification, but the cranial bones were a little more dense than usual. There was a slight increase in the cortical bone of the upper three-quarters of both femora. On September 13 an electroencephalogram showed 'a regular 8-c.p.s. alpha rhythm which blocks normally on visual attention. There are a few minor paroxysms during the resting record. On overbreathing, well-marked paroxysms of irregular 5- to 7-c.p.s. waves occur after two minutes. Impression: this is a paroxysmal record of a similar type to that seen in (idiopathic) diencephalic epilepsy.' Lumbar puncture revealed

clear fluid under a pressure of 295 mm. The serum-calcium was diminished (Table II). A Sulkowitch test of the urine (casual specimen) showed a degree of turbidity within the estimated normal range. No treatment was begun, and these investigations were repeated one week later. A further electroencephalogram showed 'an 8- to 8.5-c.p.s. alpha rhythm which blocks normally on visual stimulation. 6- to 7-c.p.s. waves are noted in all areas at random, as brief runs and as paroxysms. On overbreathing, there is an increase in the amplitude of

TABLE II
Case 2

Period	Diet		Treatment (daily)	Date	Serum chemistry		
	Calcium (gm.)	Phosphorus (gm.)			Ca (mg./100 ml.)	P (mg./100 ml.)	Total protein (gm./100 ml.)
Sept.-Oct. 1951	None	13.9.51 21.9.51 4.10.51	7.0 5.1 5.5	5.9 6.2 6.5	7.1 7.1 7.3
Oct. 5-17 1951	0.3	0.6	Calcium 2.5 gm. Dihydrotachysterol 3.0 ml. Col- loidal Al(OH) ₃ suspension 30 ml.	10.10.51 17.10.51	6.9 11.5	5.5 5.6	..
From 17.10.51	0.3	0.6	Calcium 2.5 gm. Dihydrotachysterol 1.5 ml. Colloidal Al(OH) ₃ suspension 30 ml.	24.10.51 31.10.51 7.11.51 21.11.51	9.5 11.3 11.3 9.8	5.2 6.2 5.0 6.2

the alpha wave and an increase in the slow and paroxysmal features.' The cerebrospinal fluid pressure was greater than 310 mm. of water. One week later the patient had a menstrual period, and received her usual injection of calcium gluconate. She had no tetanic cramps. On October 4 an electroencephalogram showed a tracing similar to those previously taken. Lumbar puncture showed a pressure of 310 mm. of water. In the month during which she had been under observation, without specific treatment apart from the injection of calcium at her menstrual period, she had had occasional tetanic cramps, and frequent pain and stiffness in her arms and hands. She had had no major seizures.

Treatment with dihydrotachysterol was begun on October 5. In addition calcium gluconate and colloidal aluminium hydroxide were administered, and a low-phosphorus diet was given. After five days of specific treatment she stated that she felt better, and had had no severe cramps. The same treatment was continued for a further week, after which she was feeling much better, having had no tetany since the previous visit. Her dose of dihydrotachysterol was halved. After a week of the new dosage she said that she now felt better than she had felt at any time since her thyroidectomy. She was menstruating on this occasion, but had had no tetanic symptoms, which was most unusual for her in the absence of an injection of calcium gluconate. The same treatment was maintained. One month after the commencement of specific treatment a further electroencephalogram showed 'a dominant rhythm of 9 to 10 c.p.s. There are also many 7-c.p.s. waves which occur at random. On overbreathing no significant change occurs.' A fortnight later, with no change of treatment, a further tracing was taken. The resting record was substantially normal. Combined photic-leptazol stimulation was now employed, and after a dose corresponding to 10.3 mg. per kg. of body-weight a myoclonic response occurred. A lumbar puncture was performed on the same day, and a pressure of 215 mm.

of water was found. The patient has continued to feel in excellent health, and has been free of symptoms since treatment was stabilized. Her memory has become normal, she no longer has any apparent disorders of cerebration, and she is emotionally stable. She has had no symptoms even with further menstrual periods, and has needed no further intravenous or other injections of calcium. Her nails have become normal. A lumbar puncture on December 19, 1951 still showed an elevated pressure of 205 mm. of water. This we are at a

TABLE III
Case 3

Period	Diet		Treatment (daily)	Date	Serum chemistry		
	Calcium (gm.)	Phosphorus (gm.)			Ca (mg./100 ml.)	P (mg./100 ml.)	Total protein (gm./100 ml.)
Evening of 26.3.52	Calcium 0.4 gm. intravenous, 1.5 gm. by mouth	26.3.52 27.3.52	4.6 6.1	5.9 5.4	7.2
Apr. 1952	0.3	0.6	Calcium 2.5 gm. Dihydrotachysterol: (3.4-4.4.52) 2 ml. (5.4-9.4.52) 1.5 ml. (10.4-12.4.52) 2 ml. (13.4-18.4.52) 3 ml. (19.4-13.5.52) 2 ml.	.. 7.4.52 10.4.52 15.4.52 18.4.52 6.5.52	.. 6.4 6.5 7.9 10.3 10.8 5.2 5.7 5.3 8.7 8.7 7.6
From 13.5.52	Calciferol 150,000 u.				

loss to explain, as control of her tetany has remained good. Her serum-phosphorus still remains high, of the order of 5.5 mg. per 100 ml.

Case 3. Mrs. G. C., now 43 years old, underwent operation for thyrotoxicosis five years ago. One year after thyroidectomy she developed tetany, and was treated with milk and calcium by mouth and calcium by injection. This treatment has been continued, but has never produced complete, prolonged relief of symptoms. Three years ago she began to complain of blurred vision, and at about the same time began to suffer from generalized major epileptiform fits. She had had no previous fits, nor was there a family history of epilepsy. None of her six children had had a fit. Investigation revealed bilateral papilloedema, and the provisional diagnosis of cerebral tumour was made, although there were no localizing signs. She was referred to another hospital for investigation, but in the meantime there had been a rapid development of bilateral lens opacities. Although the appearance of the fundi had thus become difficult to interpret, it was thought that papilloedema was no longer present. The cerebrospinal fluid pressure at that time, 20 months after operation, was normal. Treatment was therefore restricted to treatment of her tetany, and continued as before. Her fits continued, increasing in frequency to twice weekly. Prophylactic injections of calcium at intervals of about three days did not help, but with an increase in the dose of oral calcium the fits occurred only once a month. Bilateral extracapsular cataracts have been extracted during the past twelve months.

She was admitted to the Clinical Research Unit at the end of March 1952. Troussseau's sign was positive and Chvostek's sign negative, and there was severe hypocalcaemia (Table III). There was no papilloedema, but the edges of the optic disks were indistinct, the appearance being considered consistent with past papilloedema. Lumbar puncture was performed on three occasions before specific treatment was begun, and the pressure was always raised

(230 mm., over 300 mm., and 295 mm.). X-rays of her skull revealed a small area of calcification in the petro-clinoid ligament only. The report on an electroencephalogram stated: 'This record is characterized by a 9- to 10-c.p.s. alpha rhythm which blocks normally on visual attention. There are many irregular 4- to 7-c.p.s. waves which occur bilaterally. On overbreathing, the number of 4- to 7-c.p.s. waves increased greatly.' Except for intravenous injection of calcium gluconate, and a large oral dose, on the night of admission, no specific treatment was given until April 3 (Table III), when a low-phosphorus diet, calcium, dihydrotachysterol, and colloidal aluminium hydroxide were started. After a fortnight the serum-calcium was at a normal level, but the cerebrospinal fluid pressure was still raised (280 mm.), and the Sulkowitch test remained negative. The electroencephalographic record showed less slow activity than in the previous tracing, and the response to overbreathing was less striking. She was now free from symptoms of tetany, and was sent home to continue the same treatment. One month later she stated that she had been extremely well and completely free of symptoms. The serum-calcium was normal, and the Sulkowitch test positive. The cerebrospinal fluid pressure was still high (290 mm.). An electroencephalogram showed further improvement: 'The resting period shows an 8.5- to 9.0-c.p.s. alpha rhythm which blocks normally on visual attention. On overbreathing a few 6- to 7-c.p.s. waves are noted.' With stroboscopic flicker and leptazol no myoclonic response occurred after a dose corresponding to 9.0 mg. per kg. body-weight had been injected. The patient continued with the same treatment, except that calciferol was substituted for dihydrotachysterol.

Discussion

Papilloedema and raised cerebrospinal pressure. Although the number of reported cases is small, there appears to be no doubt that papilloedema can occur in chronic parathyroid tetany without a space-occupying lesion in the cranium. Albrecht (1923) firmly maintained this fact, quoting in support the results of post-mortem examinations in such cases. In these cases the brain was found to be generally oedematous. He thus regarded the 'choked disks' as true papilloedema, and not as papillitis. With this view most writers agree, notwithstanding that in some reports the diagnosis of optic neuritis has been suggested by the ophthalmologist (Barr, MacBryde, and Sanders, 1938; Lillie, 1945). The latter diagnosis is particularly likely to be made if loss of vision accompanies the development of papilloedema (Lyle, 1948). In most instances, however, disturbance of vision is absent or minimal. Added evidence in favour of papilloedema is that, when the cerebrospinal fluid pressure has been measured in these cases, it has almost invariably been considerably raised. In one case alone (Steinberg and Waldron, 1952) the reading was apparently normal. In another (Leonard, 1946) a single measurement of 180 mm. was recorded, which may be regarded as near the upper limit of normality. Both the raised cerebrospinal fluid pressure and the papilloedema may therefore probably be ascribed to generalized cerebral oedema. The pathogenesis of this oedema remains to a large extent obscure. It is concerned, no doubt, with a disturbance of electrolyte balance, of which the most characteristic biochemical finding is a decrease of serum-calcium. Interaction between many electrolytes is doubtless more fundamental to the development of cerebral oedema than the behaviour of

individual elements. We may find, however, a plausible if only partial explanation by considering evidence relating to calcium alone. This evidence is based on the experimental and clinical finding that deprivation of calcium has a hydrophilic effect upon tissues. Albrecht (1923) quoted an experiment in which the leg of a frog was perfused with solutions of calcium chloride. With lower concentrations the leg became oedematous, while with higher concentrations oedema did not occur. Ellis (1928) showed that acute tetany in the experimental animal caused an increase in the water-content of brain, kidney, and muscle. In children who died of infantile tetany, the water-content of the brain has similarly been shown to be significantly increased (Baar, 1928, quoted by McQuarrie, Hansen, and Ziegler, 1941). Cerebral oedema was a prominent post-mortem finding in fatal cases of tetany in the newborn (Shannon, 1931) and in older children (Dodd, Buddingh, and Rapoport, 1949). In another group of patients with tetany the calcium-content of the brain was decreased (Quest, Silvestri, and Aschenheim (1905), quoted by Albrecht, 1923). The degree of general body oedema appears to be small even in patients who have papilloedema, for none of our patients showed any significant loss of body-weight with control of the tetany. In the newborn infant general oedema may be considerable (Shannon, 1931).

Although cerebral oedema provides an adequate reason for the raised cerebro-spinal fluid pressure, an alternative explanation has been proposed. Barr, MacBryde, and Sanders (1938), in discussing their second case, said: 'Differences in concentration of calcium on the two sides of the membranes might have been contributory to accumulation of fluid during tetany, and to its disappearance after treatment.' In their patient, and in ours, the difference in concentration was of the order of 2.5 mg. of ionic calcium per 100 ml. It appears unlikely that such small differences are a sufficient cause for the increased pressure of spinal fluid. In the absence of more detailed analyses of serum and of cerebrospinal fluid, including estimations of osmotic pressure, there is not enough evidence to allow definite conclusions to be drawn. Correspondence between the serum-calcium level and the clinical manifestations of tetany is by no means close (Sevringshaus and St. John, 1943), and this lack of correlation applies equally to the production of the obvious signs of cerebral oedema; papilloedema is rare even in long-standing and severe cases of tetany. In our first patient deprivation of treatment after a long period of control produced frank tetany and epilepsy; but there was no return of papilloedema, and the cerebrospinal fluid pressure remained normal.

Associated clinical features. Of the features of special interest associated with papilloedema and tetany, epilepsy is the most common. Among the 16 recorded cases in which there is an adequate clinical history, generalized convulsions have been reported in 13 (Albrecht, 1923; Shelling and Goodman, 1934; Barr, MacBryde, and Sanders, 1938; Hurxthal, 1942; Sutphin, Albright, and McCune, 1943; Evans and Elliott, 1945; Leonard, 1946; Mortell, 1946; Berezin and Stein, 1948; Lyle, 1948; Steinberg and Waldron, 1952). Such epileptiform seizures occurred in all our patients, though only after operative interference in

the first. In this patient, with maintenance of normal serum-calcium, there were no more fits, but when specific treatment was discontinued for a time and calcium levels became subnormal, a further major fit occurred. Since resumption of control of her tetany there have been no more fits. We have not had the opportunity of observing our other two patients for a long enough period to say with certainty that maintenance of normal serum-calcium levels will completely control their fits. In the months during which their tetany has been completely controlled with oral treatment they have had no seizures.

Epilepsy is well known to occur in certain cases of tetany in the absence of papilloedema. A commonly held view is that the concurrence of the two diseases is fortuitous. The hypocalcaemia and accompanying disorders of ionic balance are then regarded as precipitating factors in persons who are idiopathic or potential epileptics (Wilson, 1940; Taubenhaus and Engle, 1945; Gotta and Odoriz, 1948). I shall discuss this point further in the section on electroencephalography, in the meantime mentioning some suggestive clinical evidence in favour of a contrary hypothesis. When fits and tetany occur together, it is invariably found that measures which adequately control tetany also completely control the fits. This is so in any age-group, whether in neonatal life (Bakwin, 1939), in childhood (Sutphin, Albright, and McCune, 1943), in adolescence (Himsworth and Maizels, 1940), or in adult life (Scarlett and Houghtling, 1944). In cases in which tetany alone was relieved it appears that treatment may have been less than adequate (Shelling and Goodman, 1934). These findings may, of course, be due solely to the removal of the precipitating factor, namely the condition of tetany. If this is the whole explanation it is interesting that the epilepsy cannot be controlled by anticonvulsant drugs, but only by relief of tetany (Kowallis, 1941), and that, on the other hand, relief of tetany abolishes the need for further anticonvulsant treatment (Eaton and Haines, 1939; Taubenhaus and Engle, 1945). The exact basis of the fits is still obscure. I relate them tentatively to the mechanism suggested in the case of papilloedema, namely the development of cerebral oedema. This view agrees with the conclusions of McQuarrie, Hansen, and Ziegler (1941). A similar mechanism is seen in the production of epilepsy in experimental animals by massive intragastric administration of water (Rowntree, 1923) and in the water-pitressin test used in the diagnosis of idiopathic epilepsy (Garland, Dick, and Whitty, 1943). Fremont-Smith, Merritt, and Lennox (1932) considered that the effect of pitressin-hydration in producing fits is not dependent upon an increase of cerebrospinal fluid pressure *per se*. In patients who have tetany and epilepsy such an increase is certainly not invariable.

In our second patient the tetany and the fits were apt to be worse during menstruation. A close association between menstruation and epilepsy has frequently been observed, and is presumably related to water-retention occurring before and during the menses (Burnett, 1946). In the same patient pregnancy seems to have lessened the tendency to convulsions. This effect may be attributed to activity of the parathyroid tissue of the foetus (MacCallum, 1924). Lactation is known to aggravate both epilepsy and tetany in certain patients

(Stander, 1945). The aggravation is no doubt due to loss of calcium in the maternal milk, and may have been a factor in our patient, at any rate after the birth of her second child. We may again note that, as in the case of papilloedema, there appears to be no exact correlation between other manifestations of tetany and the occurrence of generalized convulsions. Nor does the duration and severity of tetany seem to bear any direct relation to the incidence or frequency of fits. In the newborn the appearance of tetany and fits may be nearly or quite simultaneous, whereas some patients with tetany of long standing never have epileptic seizures. The level of the serum-calcium, either at different times or in different patients, is no certain guide to the liability to convulsions (McQuarrie, Hansen, and Ziegler, 1941).

Electroencephalography. In chronic parathyroid tetany, with or without the occurrence of fits, there may be an abnormality in the electroencephalogram which is reversible with appropriate treatment (Odoriz, del Castillo, Manfredi, and de la Balze, 1944; Gotta and Odoriz, 1948). According to these authors the characteristic picture comprises little alpha rhythm, an increase in the amount of fast activity, simple spikes, and some slow waves of six to seven cycles per second (sometimes two to five cycles per second), mainly in the frontal areas. There is an excessive sensitivity to hyperpnoea, which may be compared to the clinical finding that overbreathing may make latent tetany manifest. The same authors found, however, that even after treatment, when the electroencephalogram had reverted to normal with the return of a well-defined alpha rhythm and inappreciable amounts of fast and slow activity, overbreathing brought out the original hypoparathyroid picture. In the patients reported here, and in a fourth patient who had fits and tetany but no papilloedema, we found nevertheless that when the hypoparathyroidism was properly controlled overbreathing was without effect on the electroencephalogram. It is possible that overbreathing will only bring out abnormalities in a patient with a normal resting record if control of the tetany is less than adequate. We found in such patients that early in their course of treatment hyperpnoea would, in fact, cause the appearance of waves characteristic of uncontrolled tetany. About a week later, with maintained clinical and biochemical control, no such effect could be elicited.

Electroencephalography has been performed previously in only five cases of tetany with papilloedema (Sutphin, Albright, and McCune, 1943; Mortell, 1946; Levy, 1947; Berezin and Stein, 1948; Steinberg and Waldron, 1952). Other workers have confirmed the amelioration in the record after treatment in patients without papilloedema (Kowallis, 1941; Taubenthal and Engle, 1945; Simpson, 1952). The tracing in tetany is often reported as showing evidence of epilepsy or tumour, for its only specificity lies in the response to treatment. There is no exact correlation between the serum-calcium and the electroencephalogram. The duration of a particular level of serum-calcium is more important than the figure estimated at the time of electroencephalography. We have confirmed in another patient the fact that the tracing will not become normal during treatment of an acute attack by intravenous calcium, even

though symptomatic relief has been complete (Gotta and Odoriz, 1948). Improvement, therefore, cannot depend solely on an increase in calcium-ion concentration, even though experimentally such an increase is known to inhibit the electrical activity of the cortex (Heppenstall and Greville, 1950). Cerebral oedema may be invoked as a cause of the abnormal tracing, acting more through tissue-electrolyte changes than increased water-content (Fremont-Smith, Merritt, and Lennox, 1932; Williams, 1939). The relatively slow return to normal may thus be associated with intracellular mechanisms such as the metabolism of creatine phosphate (Imrie and Jenkinson, 1933; McIlwain and Gore, 1951). Whatever the biochemical explanation may be, a normal record will not be obtained until a normal serum-calcium has been maintained for a few weeks.

To elucidate further the nature of the fits occurring in our patients, we employed the technique of simultaneous electroencephalography and photic-leptazol stimulation (Gastaut, 1950). The electroencephalograms of our patients were first restored to normal, and the myoclonic thresholds then determined. All three patients gave threshold values in the normal range, and well above that within which the threshold values lie in the majority of idiopathic epileptics. I therefore venture the hypothesis that they are not potential or idiopathic epileptics, but have basically normal brains. There are, however, certain features in the first two patients which militate against such a view. In Case 1 all four children were subjected to electroencephalography. Three gave normal tracings, but the fourth showed a dysrhythmic record. In Case 2 the patient gave a history of infantile convulsions. On the other hand all her four children had normal electroencephalograms. The number of patients reported here is far too small to allow a dogmatic opinion. There is rather more evidence in favour of the view that these patients, in the absence of hypoparathyroidism, have a normal cerebral function, than there is in favour of their being true epileptics.

Psychosis occurs with relative frequency in tetany (Greene and Swanson, 1941), and has been reported four times in association with papilloedema (Barr, MacBryde, and Sanders, 1938; Leonard, 1946; Mortell, 1946; Lyle, 1948). In the first patient of the present series, although a preceding history of psychic disturbance made assessment difficult, there seemed little doubt that an improvement of mental status occurred with the control of the tetany. In the second patient there was full restoration to normal mentality.

Intracerebral calcification in association with papilloedema and tetany has been reported thrice (Leonard, 1946; Mortell, 1946; Steinberg and Waldron, 1952). It did not occur in any of our patients. *Lenticular cataract* was reported in eight of the 16 adequately reported cases in which there was papilloedema (Albrecht, 1923; Barr, MacBryde, and Sanders, 1938; Sutphin, Albright, and McCune, 1943; Evans and Elliott, 1945; Lillie, 1945; Lyle, 1948; Steinberg and Waldron, 1952). It occurred in our second and third patients, necessitating bilateral lens extractions. Disorder of *ectodermal structures* is comparatively common in hypoparathyroidism (Learner and Brown, 1943); but in the series reviewed in the present paper the hair or nails were affected in only four cases

(Sutphin, Albright, and McCune, 1943; Evans and Elliott, 1945; Berezin and Stein, 1948; Collins-Williams, 1950). There was ridging of the finger- and toenails in our second patient, but otherwise no sign of ectodermal disorder occurred.

Treatment

Many patients with chronic parathyroid tetany seem to become accustomed to a lowered serum-calcium, and may be free of symptoms for long intervals (Kowallis, 1941); but it appears probable that such patients are in fact undergoing a progressive and possibly irreversible deterioration. Once the diagnosis of chronic hypoparathyroidism is made, specific treatment must be instituted until symptomatic and biochemical control is achieved. Thereafter it is important that both the patient and his medical attendant should realize that maintenance treatment is necessary and must be lifelong, or relapse will be certain. Treatment with calcium salts alone is not satisfactory, nor, except perhaps in acute tetany, is treatment with parathyroid hormone. Adequate treatment demands the use of calciferol or dihydrotachysterol. It has been claimed that the one or the other substance is the drug of choice, but in the doses necessary in chronic tetany their pharmacological effects are similar. Because of its more rapid action, dihydrotachysterol is perhaps the better drug to use in the early stages of treatment. Its effect is more transient than that of calciferol, and the latter may therefore be of more value in maintenance of control (Albright, Bloomberg, Drake, and Sulkowitch, 1938). Cost is perhaps a good guide to choice, and at present prices in Australia (1952) dihydrotachysterol in equivalent dosage is about five times as expensive as calciferol. Dosage is largely an individual matter, but in the author's experience the initial dose of dihydrotachysterol recommended by Albright and Reifenstein (1948) is somewhat too low. As prolonged treatment with either of these steroids will lead in time to decalcification of the skeleton (Albright and Sulkowitch, 1938), it is necessary to administer extra calcium in the diet. Powdered calcium lactate, or preferably gluconate, in a dose of the order of 24 gm. (about 2.5 gm. of calcium), should be dissolved in hot water, and the resulting solution drunk during the day (Haines, 1940; Rose, 1943). It is more palatable if iced. Calcium chloride has been recommended as the vehicle of choice (Sevringshaus and St. John, 1943), but Albright and Reifenstein (1948) have condemned its use on the ground that long-continued therapy leads to a renal disorder, with hypercalcuria at low serum-calcium levels. Experimental evidence seems to indicate that calcium gluconate, lactate, and chloride are equally effective in raising the serum-calcium level, the effect depending only on the calcium content of the dose (Greenberg, Gunther, Dalton, and Cohn, 1932).

Many authors have urged the advantages of a low-phosphorus diet in the management of chronic tetany (Ellsworth, 1933; Shelling and Goodman, 1934; Anderson and Lyall, 1939; Cantarow, Stewart, and Morgan, 1939; Rose, 1943). Although such a diet is sometimes said to be unpalatable and to lead to vitamin deficiencies, this need not be so, as it is not necessary to make it excessively

rigid. Milk should be proscribed except in minimal quantities, and cheese, meat, and eggs eaten in moderate amounts only. Milk is often recommended to patients with tetany on account of its high calcium content; but because of its high phosphorus content it frequently does more harm than good, and may lead to exacerbation of the disorder (Cantarow, Stewart, and Morgan, 1939). In order to decrease phosphorus absorption from the alimentary canal, colloidal aluminium hydroxide may be given (Fauley, Freeman, Ivy, Atkinson, and Wigodsky, 1941).

Albright (1939) suggested that a patient with chronic tetany may be treated like a diabetic. This involves training the patient to test his urine with the Sulkowitch reagent (Barney and Sulkowitch, 1937). Albright (1941) has said that below a serum-calcium level of approximately 7.0 to 7.5 mg. per 100 ml. no calcium, detectable clinically by this reagent, will appear in the urine, and that therefore frequent serum-calcium determinations are unnecessary. We do not agree with this view, and other authors have also found the test unreliable (Sevringshaus and St. John, 1943; Jordan and Kelsall, 1951). In our second patient a precipitate within the normal range of density was obtained with the Sulkowitch reagent when the serum-calcium was less than 7 mg. per 100 ml. In our third patient a negative test continued to be obtained even after the serum-calcium had reached a normal level. The Sulkowitch test would have been of little value in gauging treatment in these cases. None of our patients, it may be added, showed any evidence of grossly defective renal function by ordinary clinical tests. We consider that nothing can replace clinical assessment of the patient, coupled with determinations of the serum-calcium as frequently as is considered desirable.

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Summary

A review is presented of previously recorded cases of the syndrome, papilloedema in chronic parathyroid tetany, with a report of three new cases. Reference is made to the frequent confusion with cerebral tumour and idiopathic epilepsy. The ready response to adequate specific treatment and the necessity for continued watchful management are emphasized.

An attempt is made to provide an explanation, on a common basis, of the occurrence in hypoparathyroidism of electroencephalographic changes, epileptiform seizures, and raised intracranial pressure.

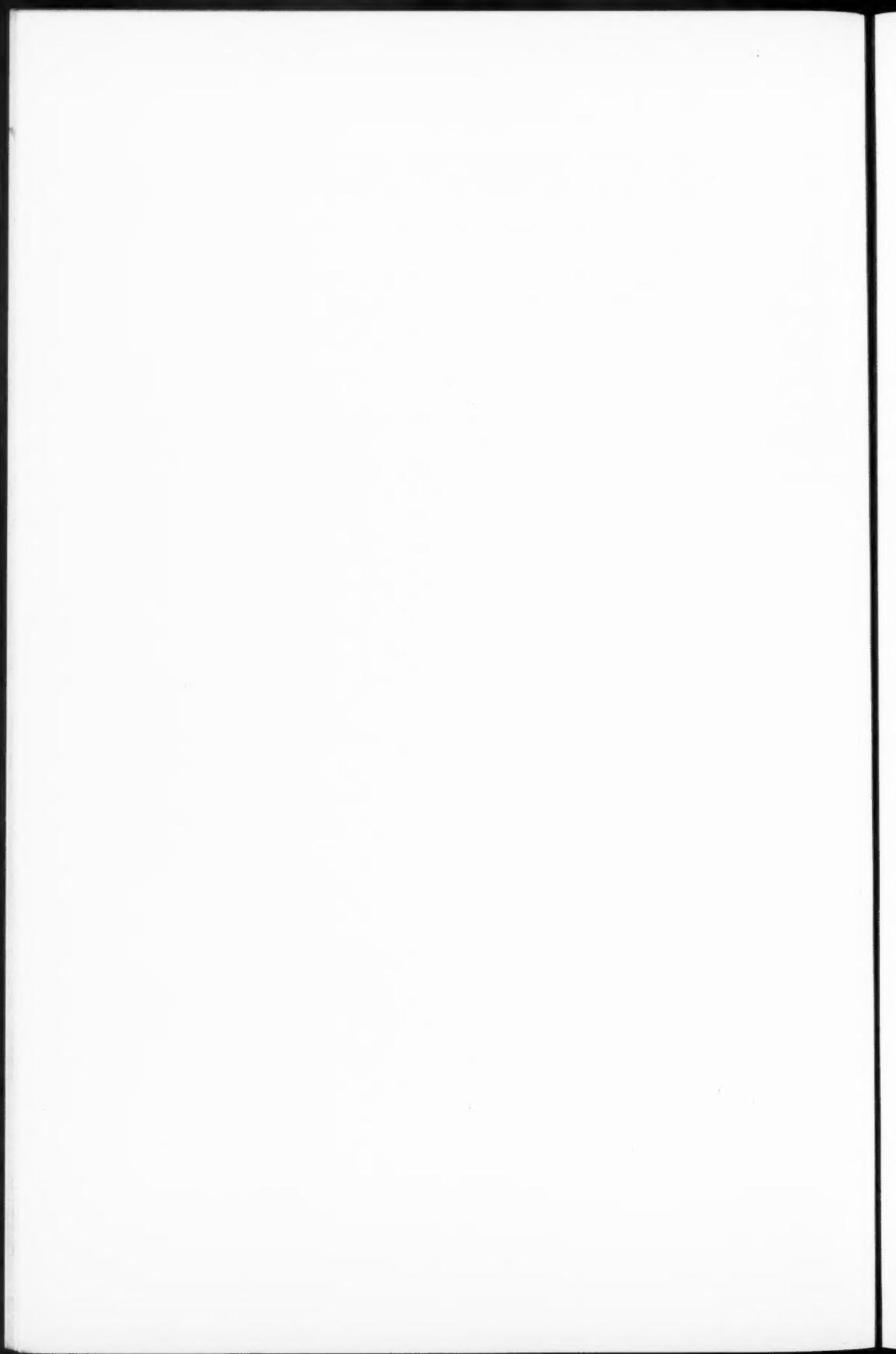
The mechanism of fits and electroencephalographic changes in such patients is further discussed, with mention of the possible value of determination of the 'myoclonic threshold'. Evidence is presented that the three patients personally observed, all of whom had major epileptiform convulsions when inadequately treated, were not suffering from idiopathic epilepsy.

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CHOLECYSTOGRAPHY¹

Observations on the Technique of the Examination and the Interpretation of its Results

By I. R. S. GORDON

(From the Department of Radiodiagnosis, United Bristol Hospitals)

THE purpose of the present paper is twofold: first to review and assess the technique of cholecystography, and secondly to attempt to estimate the significance of its results in terms of disordered gall-bladder function and of pathological conditions affecting the biliary system. Cholecystography consists in rendering the gall-bladder opaque to X-rays by the administration of a substance which contains atoms of adequate atomic weight, is secreted by the liver in the bile, and is increased in concentration when water is absorbed from the bile in the gall-bladder. Its possibility was foreshadowed in 1909, when Abel and Rowntree observed that phenolphthalein was excreted by the liver, but it was not until 1924 that Graham and Cole succeeded in producing visualization of the gall-bladder by the use of tetrabromphenolphthalein. This compound was soon replaced by the corresponding iodine derivative, which remained the standard preparation until 1940, when Dohrn and Diedrich introduced an iodine-containing derivative of phenylpropionic acid, variously known as pheniodol, biliselectan, or priodax. This compound has now replaced tetraiodophenolphthalein in routine practice for oral cholecystography, though the latter substance is still used when the intravenous route is required, since pheniodol causes severe toxic symptoms when given in this manner.

The technique generally adopted at the present time for oral cholecystography consists in taking a preliminary film of the right upper quadrant of the abdomen, and then giving 3 gm. of pheniodol by mouth. The patient then goes to bed, and takes no further food before coming to the X-ray department 16 hours later. Films are then taken and inspected to ascertain whether the gall-bladder is visualized. If visualization has occurred further films are taken, if required, to demonstrate any special points, and then a meal containing fat is given. Films are then taken at intervals to study the contractility and emptying-rate, and to demonstrate the bile-ducts. If there is no visualization, it is common practice to give a further dose of pheniodol later the same day, and to take films 16 hours after this second dose. These may show visualization to have occurred, or may give a more definite outline of the gall-bladder in the case of a previously doubtful shadow. This method should demonstrate (1) whether visualization has occurred and, if so, the density of the shadow obtained, from which an inference may be drawn as to the normal or abnormal

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function of the gall-bladder; (2) the site, shape, and size of the gall-bladder, and possibly of the cystic and common bile-ducts; (3) the presence of gall-stones, when invisible on the plain film owing to the absence of calcium in the calculus; and (4) the rate of filling or emptying, and the power of contractility, of the gall-bladder.

Satisfactory visualization of the gall-bladder depends on the following factors: (1) Absorption of the contrast medium from the alimentary tract, unless it is given intravenously. (2) Transport of the contrast medium via the portal vein to the liver. (3) Its secretion by the liver-cells into the bile. (4) Passage of the contrast medium into the gall-bladder. This depends on the normal physiological mechanism of filling of the gall-bladder, and is the result of a combination of the secretory pressure of the liver (capable of reaching 300 to 360 mm. of water according to Newman (1933)) and the resistance of the closed sphincter of Oddi, which prevents the bile from flowing into the duodenum. (5) Concentration of the bile by the action of the gall-bladder mucosa. The normal concentrating power of the mucosa may or may not be lost when the gall-bladder is diseased. (6) Adequate radiography. Owing to the small difference in contrast between the pheniodol in the gall-bladder and the surrounding tissues, high-quality films should be used, with a careful attention to exposure factors. As short an exposure as possible is necessary to minimize the risk of blurring due to movement. Good radiography is especially important in view of the well-recognized tendency for gall-bladder disease to occur in obese subjects. A slight degree of obliquity, with the patient's right side lifted away from the film, is normally desirable to ensure that the gall-bladder shadow is not overlying the spine; but it is important to realize that considerable variation may occur in the position of the gall-bladder, since failure to include the gall-bladder on the film may be mistaken for evidence of disease. Robinson (1941) suggested that patients of an asthenic build may require to be rotated rather more into the left anterior oblique position than patients of more normal build; those of a markedly hypersthenic build may even require to be rotated in the opposite direction, with the left shoulder lifted away from the film. The possibility of a left-sided gall-bladder, as part of a general situs inversus, can also occasionally lead to trouble. Pendergrass and Hodes (1935) suggested that a 17 in. \times 14 in. film, covering the whole abdomen, should be taken, so that not only will the gall-bladder be included wherever it may lie, but a view of other intra-abdominal organs and the diaphragm can be obtained. A film taken in the erect position is useful, and should be included in the routine examination, since it may show the presence of stones floating on the bile, may help in differentiating papillomata from stones, and may show whether deformities are due to adhesions to neighbouring organs. The obliteration of the gall-bladder shadow by gas in the hepatic flexure may be minimized by the use of a horizontal ray with the patient lying on the right side, as described by Kirklin (1948). In this position the gall-bladder tends to move downwards and the intestines upwards. Personal experience tends to show, however, that the mobility of the hepatic flexure and the gall-bladder is small in the obese, hypersthenic type of patient.

Technique

Cholecystographic agents. Pheniodol has superseded sodium tetraiodophenolphthalein for the oral test because of the following advantages. Reactions to its use are not so severe, and absorption is therefore more consistent and the percentage of faint or doubtful shadows is less; elimination is mainly by the kidneys, rather than by the colon as is the case with tetraiodophenolphthalein, so that shadows which may obscure the cholecystogram are avoided. The main disadvantages reported in the use of pheniodol are its toxicity on intravenous injection, and a tendency, greater than that of tetraiodophenolphthalein, to inhibit emptying of the gall-bladder, as Copleman observed in 1946. The optimum requirements of a cholecystographic agent, and their relation to its chemical structure, have been enumerated by Epstein, Natelson, and Kramer (1946) as follows: (1) Iodine-content adequate to provide a sufficiently dense radiographic shadow. (2) A molecular structure which is selectively absorbed by the liver-cells, such as the phenol group which is normally detoxicated in the liver. (3) Fat-solubility, to prevent excessive excretion by the kidney; this can be ensured by the length of the aliphatic side-chain in the molecule. (4) Solubility in bile, which is facilitated by the presence of a carboxyl group, enabling a sodium salt to be obtained. (5) Low toxicity, depending on the paucity of phenol groups in the molecule. Certain other compounds which have been tried recently for cholecystography exhibit features of interest. 'Monophen', hydroxydiiodobenzyl-cyclohexanoic acid, described by Wasch and Epstein (1951), has only one phenol group, and toxic effects, especially diarrhoea, are stated to be less marked than with pheniodol, opacification being satisfactory in doses of 4 gm. 'Telepaque', 3-(3-amino-2, 4, 6-triiodophenyl)-2-ethylpropanoic acid, containing 66.7 per cent. of iodine by weight, also possesses only one phenol group, and was stated by Christensen and Sosman (1951) to be less liable to give rise to nausea and diarrhoea than pheniodol, 78 per cent. of patients having no symptoms at all. The high iodine-content results in dense shadows, and for this reason the authors suggested that a dose of 2 gm. may be sufficient. Elimination is almost entirely by the colon rather than the kidney, resulting in troublesome bowel shadows.

Dosage. It is routine practice to give 3 gm. of pheniodol for the oral test, but doses up to 6 gm. are generally regarded as safe. For children a dose varying with body-weight is used: 0.15 gm. per kg. for children under four years, and 0.05 gm. per kg. for those over four years, the technique being otherwise similar to that used in adults (Hrdlicka, Watkins, and Robb, 1945). For the intravenous test with tetraiodophenolphthalein an average dose of 3 gm. is usually recommended, given diluted with 40 to 50 ml. of saline or distilled water, and either injected slowly into a saline drip or washed through with saline to minimize the risk of thrombosis of the vein. Feldman (1948) suggested varying the dose according to the body-weight, and recommended 0.05 gm. per kg. as a suitable dose. The present writer has no personal experience of this test, but believes that it may be useful when there is doubt as to the adequate absorption of

pheniodol by mouth. A variation of the oral dose for adult patients according to body-weight seemed to be a reasonable procedure, and in the present investigation the opportunity was taken to compare a series of consecutive cases in which this was done with a series in which a standard dose of 3 gm. was given. A simple scheme of dosage was employed, using 3 gm. for all patients whose body-weight was below 10 stone, 4 gm. for those between 10 and 13 stone, 5 gm.

TABLE I
Comparison of Results Obtained with Constant and Variable Dosage of Pheniodol

	<i>Series I</i> Constant dosage (3 gm.)	<i>Series II</i> Variable dosage (3 to 6 gm. according to body-weight)
Shadow of normal intensity	98 (65.5%)	73
Faint shadow with no evidence of gall-stones	12 (8%)	3
Faint shadow with evidence of gall-stones	7 (4.5%)	6
No shadow obtained	33 (22%)	18
Number of cases	150	100

TABLE II
Incidence of Reactions with Increase in Dose of Pheniodol

<i>Body-weight and dose</i>	<i>Number of patients</i>	<i>Number of patients with diarrhoea or vomiting</i>
Below 10 stone (3 gm.)	46	20 (43%)
Between 10 and 13 stone (4 gm.)	44	29 (66%)
Between 13 and 16 stone (5 gm.)	9	8 (88%)
Over 16 stone (6 gm.)	1	1 (100%)
Total	100	58

for those between 13 and 16 stone, and 6 gm. for those over 16 stone. The results are given in Tables I and II. It will be seen that there was an appreciable reduction in the percentage of cases in which a faint shadow was obtained without radiological evidence of gall-stones, the group of results which is notoriously the most difficult to interpret. This reduction was held to justify the increase which occurred in the liability to reactions, mostly in the form of diarrhoea.

Reactions. Most authorities are in agreement that reactions to pheniodol are less frequent and less severe than those experienced with tetraiodophenolphthalein. The commonest symptom is diarrhoea, but nausea, vomiting, a burning sensation in the throat on swallowing the drug, and transient burning sensations on micturition also occur. Some patients complain of feeling faint and of colicky abdominal pain, usually in association with diarrhoea. Albuminuria has also been reported by various authors, but there is reason to believe, as Seedorf, Powell, Greenlee, and Hartman (1950) have shown, that the substance causing a precipitate on boiling the urine is not albumin but pheniodol itself, which appears in the urine fairly rapidly after ingestion, up to 80 per cent. of the dose given being recoverable from the urine within 72 hours. These authors suggested that pheniodol never causes harm to the kidney. After

sodium tetraiodophenolphthalein has been given intravenously there may be generalized aching pains or headache, and occasionally more severe symptoms such as syncope, vomiting, and a fall in blood-pressure. Phlebitis may occur if the injection is made too rapidly. Adrenaline or glucose should be given if severe reactions occur. Figures indicating the incidence of reactions with tetraiodophenolphthalein and pheniodol are given in Table III. In the present

TABLE III
Reactions with Pheniodol and Tetraiodophenolphthalein

	Number of cases	Dose (gm.)	Nausea alone (%)	Vomiting (%)	Slight (%)	Diarrhoea Consider- able (%)	Dysuria (%)	No reaction (%)
<i>Tetraiodophenolphthalein:</i>								
Paul and Pohle (1944)	80	3.5	45	5	14	15	0	..
Unfug (1946)	..	3.5	68	8	22	28	4	24
<i>Pheniodol:</i>								
Paul and Pohle (1944)	114	3	28	1.7	11.5	11.5	15	..
Unfug (1946)	50	3	32	2	16	20	20	38
Fong (1946)	250	3	23	1	33	10	50	14
Present series	170	3	Not asked	5	15	21	Not asked	57

TABLE IV
*Results and Reactions with Different Preparations of Pheniodol
(Dose 3 gm.)*

Results:	Suspension	Tablets	Granules
Shadow of normal intensity	66%	72%	68%
Faint shadow	12%	9%	12%
No shadow	22%	19%	20%
<i>Reactions:</i>			
Vomiting	6%	0	12%
Diarrhoea (Slight Considerable)	11% 17%	28% 40%	20% 32% 52%
'Burning in throat'	67%†	25%‡	67%§
No diarrhoea or vomiting	64%	56%	44%
Number of cases	83	62	25

* 28 patients interrogated. † 4 out of 6. ‡ 4 out of 16. § 4 out of 6.

investigation nausea and dysuria were not specifically inquired for, but were stated to have occurred in 5 per cent. and 2 per cent. of cases respectively. 'Burning in the throat' was noticed by 12 (43%) of 28 patients (including patients who were given different preparations of pheniodol) who were asked about this symptom. Pheniodol is dispensed as an aqueous suspension, as tablets, and as sugar-coated granules, and the opportunity was taken to see whether there was any significant variation in the results obtained, or in the reactions experienced, with these three types of preparation. The data are shown in Table IV. It will be seen that while there is no significant variation in the results obtained with the three types of preparation the tablets and suspension appear to be less liable to cause reactions than the sugar-coated granules, the tablets being more liable to cause diarrhoea, and less liable to cause vomiting, than the suspension. It has already been pointed out that the

incidence of reactions is considerably increased by higher dosage. The importance of reactions to oral pheniodol lies less in the danger or discomfort, which are not great, than in the possibility that they may interfere with the absorption of the drug from the intestine and so give rise to misleading results. The two symptoms likely to cause trouble in this way are diarrhoea and vomiting. The latter, if it occurs within three or four hours of taking the pheniodol, will

TABLE V
Diarrhoea after Pheniodol

Number of cases analysed	37
Number of motions: mean 3.8	{ Three or less	.	.	19 cases	
					More than three	.	.	18 "	
Abdominal pain present with diarrhoea	13 "	
					Site	Lower	.	6 "	
						Central	.	3 "	
						Upper	.	2 "	
						Generalized	.	2 "	
Time of onset after taking pheniodol: mean 8.3 hours*	{ Three hours or less	.	3 "		
					Between 3 and 10 hours	.	18 "		
					More than 10 hours	.	16 "		

* With dose of 3 gm. (15 cases): mean 10.9 hours
" " 4 " (16 "): " 7.4 "
" " 5 " (6 "): " 4.2 "

TABLE VI
Effect of Diarrhoea and Vomiting on Results Obtained

	All cholecystograms	With diarrhoea only	With vomiting only	With diarrhoea and vomiting
Shadow of normal intensity	288 (72%)	76 (65%)	5 (100%)	5 (56%)
Faint shadow	41 (10%)	15 (13%)	0	3 (33%)
No shadow	71 (18%)	26 (22%)	0	1 (11%)
Total	400	117	5	9

probably result in a significant reduction of the amount absorbed, necessitating a repetition of the examination or recourse to the intravenous test. Vomiting, however, may occur as a result of the patient's disease, and may be compatible with normal absorption, especially if it does not occur until the following morning. It is the present writer's belief that diarrhoea (Table V) does not often interfere with the absorption of pheniodol, since it is due to the action on the large intestine of that portion of the pheniodol which has not been absorbed higher up. This view is based on the following grounds. First, pheniodol is known to be excreted, after absorption, by the kidneys rather than the colon. Secondly, the diarrhoea occurs usually between five and 15 hours after the pheniodol is taken by mouth. Thirdly, abdominal pain, if present, tends to be noticed mainly in the lower part of the abdomen. Fourthly, the action of pheniodol in producing diarrhoea is likely to be analogous to that of phenolphthalein, since it probably owes its toxicity to the phenol group, and this drug is known to exert its action on the large bowel. If this is so, the diarrhoea is unlikely to lessen the time available for absorption, or to interfere with the

absorptive function of the small intestine. It also seems reasonable to assume that absorption has normally occurred in most cases before the onset of the diarrhoea. It can, of course, be argued that the presence of diarrhoea means that an unduly high proportion of the pheniodol has escaped absorption and has been passed on to the large intestine, but experience shows that, among patients suffering from diarrhoea after pheniodol, the proportion in whom satisfactory visualization is obtained is only slightly reduced (Table VI). It is concluded that the presence of diarrhoea should not be held to indicate failure of absorption unless it occurs within three hours of the administration of the drug, or is associated with vomiting or radiological evidence of unabsorbed pheniodol in the colon. On the other hand, its presence may aid in securing adequate radiographs by the removal from the colon of faeces and gas, which might otherwise obscure the gall-bladder shadow.

Contra-indications to cholecystography. The oral test is not practicable in the presence of complete gastric stasis due to pyloric stenosis or other causes, or of persistent vomiting, since absorption of the drug cannot be achieved. In such a case the intravenous test seems to be justifiable and should give good results. Since pheniodol is excreted mainly by the kidneys, renal failure is a contra-indication to its use. Liver disease need not be regarded as a contra-indication, since there is little evidence that pheniodol is toxic to the liver; furthermore, as will be shown later, normal gall-bladder shadows can be obtained in the presence of considerably reduced liver function. In view of the greater liability to circulatory collapse attending the intravenous use of tetraiodophenolphthalein, this form of test should not be carried out in the presence of myocardial disease, arteriosclerosis with a normal or low blood-pressure, or advanced pulmonary or hepatic disease.

Preparation of the patient. Faeces or gas in the intestine may obscure the outline of the gall-bladder; a purgative or an enema may be used to empty the bowel, or 0.5 ml. of pitressin to remove gas, but such measures are not normally necessary; the pheniodol itself may help if it induces diarrhoea. The normal filling of the gall-bladder depends on the contraction of the sphincter of Oddi, which may be interfered with if food is taken between the administration of the drug and the time that the films are taken; alkalinization of the stomach by means of sodium bicarbonate is said to aid in keeping the sphincter closed (Kerley, 1950). Considerable controversy exists as to whether it is desirable to allow fat during the few days prior to the test. It was alleged by Delario (1931) that fat interferes with the absorption of tetraiodophenolphthalein, but there is no evidence available as to whether this is true of pheniodol. Kirklin (1931) considered that giving fat prior to the test decreased its accuracy by 25 per cent., and might interfere with filling by causing contraction of the gall-bladder and relaxation of the sphincter of Oddi. There is, however, a considerable body of opinion which favours the administration of a fatty meal before the examination. Brewer (1947) considered that misleading results due to physiological stasis of the gall-bladder, which may prevent filling and concentration of the pheniodol, can be avoided if a fatty meal designed to

empty the gall-bladder is given on the day previous to the test. He suggested that this should be done in any case in which the gall-bladder shadow is faint or absent and there is a history of vomiting, limited food intake, or a fat-free diet. Curl (1942) also made some interesting observations on a series of normal students, in which he showed that the proportion of cases in which the gall-bladder was not visualized after oral tetraiodophenolphthalein was significantly higher in subjects who were given a low-fat diet prior to the test, and was reduced by the administration of a high-fat diet. Kerley (1950) and Feldman (1948) both advised the use of a fatty meal three hours before commencing the test. The present writer does not consider, on the basis of the opinions quoted above, that a fatty meal should be used as a routine measure before cholecystography, but believes that when the double-dose technique is employed, that is in cases in which the gall-bladder is not clearly visualized, it is reasonable to give the normal fatty meal after the first test in spite of non-visualization, and then proceed to the further dose of pheniodol the same evening. Vitale (1947) observed that in certain cases visualization of the gall-bladder, if absent on the 16-hour film, might occur two to ten minutes after giving water or other food (a procedure which he termed the 'water test'). If this view is correct it suggests that it may be justifiable, not only to give the fatty meal in such cases, but to take a film one hour afterwards in the usual way.

The double-dose technique. Many varieties of this technique have been described. Its results demonstrate the occurrence of cases in which visualization is obtained after the second dose, though such cases seem to have occurred much less frequently with pheniodol than with tetraiodophenolphthalein. As has been stated above, it is probably good practice to give a fatty meal after the first dose, whether it is decided to employ a double dose or not. The results obtained with this method in 48 cases in the present series are summarized in

TABLE VII
Results of the Double-Dose Technique

The method was used in 48 cases (14%) in a series of 353 consecutive cholecystograms	
Second examination with unaltered result	34 cases (71%)
{ Faint shadow	1 case
{ No shadow	33 cases
Second examination with altered result	14 ,, (29%)
{ No shadow to faint shadow	8 ,,
{ No shadow to normal shadow	2 ,,
{ Faint shadow to normal shadow	3 ,,
{ Faint shadow to no shadow	1 case

Table VII. The dose in most cases was similar to that given on the first day; occasionally a slightly increased dose was used on the second day.

Demonstration of bile-ducts. This can often be achieved as the result of cholecystography, and may occasionally be of value in interpretation, as will be shown later. It appears to be rather less easy with pheniodol than with

tetraiodophenolphthalein, since according to Copleman (1946) pheniodol acts like a sympathetic mimetic drug, and causes inhibition of gall-bladder emptying, and it is necessary to employ serial radiography during the emptying phase if the ducts are to be visualized in more than a small proportion of cases. In 100 consecutive cholecystograms in which films were taken as a routine one hour after the fatty meal, the ducts were visualized, often very incompletely, in only 21 cases. Feldman (1948) recommended taking films in the 20° left anterior oblique projection 10 minutes after the fatty meal is given, and at five-minute intervals thereafter, until satisfactory visualization is obtained. Fluoroscopy may also be employed, but it is difficult owing to the poor contrast obtained. The ducts are not normally all visible in a single film.

Interpretation

I. Cholecystography and gall-bladder function

Cholecystography, besides being a method of obtaining a photographic record of the structural features of the gall-bladder, bile-ducts, and their contents, also constitutes a test of gall-bladder function. The former use, which it shares with every other type of radiographic investigation, is of relatively minor importance apart from the demonstration of gall-stones. The latter is of more importance as providing evidence of gall-bladder disease, but is more difficult of interpretation, because the evidence is not direct, as is the case in most radiographic work, but only implies the existence of disease by revealing disordered function. Although interpretation is more difficult, this is not necessarily a disadvantage. Cholecystography allows the detection of either a disorder of function or an abnormality of structure, or both; furthermore, it is probable that in the evolution of disease disordered function precedes structural abnormality, and may in some diseases constitute the sole feature. It seems therefore that such a method may make it possible to diagnose disease in its earlier stages. There are, however, serious limiting factors in our present state of knowledge and technique. First, as a test of function, cholecystography is not very delicate, and may almost be regarded as a test of failure rather than of function; the gall-bladder, like most other organs, has considerable reserve powers, and can continue to perform its functions even in the presence of considerable damage. Secondly, our knowledge of the normal function of the gall-bladder, and of the means by which it is controlled, is as yet confused and scanty, and that of the abnormalities to which it may be subject even more so.

Normal gall-bladder function. The known functions of the gall-bladder are absorptive, secretory, and motor. Absorption of water and salts is the function of the mucosa of the body and fundus, and is responsible for the concentration of the bile. Secretion is carried out by the glands of the infundibulum and neck, and results in the addition of about 20 ml. of mucus to the bile per day. The motor function of the gall-bladder is carried out by the smooth muscle of its wall and of the wall of the bile-ducts. Such muscle is mainly concentrated at the opposite ends of the biliary tract, in the fundus of the gall-bladder, and

in the ampulla of Vater where the common bile-duct passes through the wall of the duodenum. The muscle is controlled by the autonomic nervous system and by cholecystokinin, a hormone analogous to secretin elaborated in the wall of the duodenum in response to acid or food. Ivy (1947) considered that in normal circumstances cholecystokinin is the main factor responsible, but it is highly probable that disorder of the motor functions, in the absence of gall-bladder disease, is a result of abnormal autonomic activity.

Criteria of abnormal function. The following criteria are at present employed in cholecystography to detect abnormalities of gall-bladder function:

1. *Intensity of the shadow obtained.* This is used as a test of absorptive function. Assessment is necessarily subjective, but some help may be obtained in classifying the results by the use of neighbouring structures, such as the ribs or transverse processes, for comparison. But before faintness or absence of the gall-bladder shadow can be adduced as evidence of faulty concentrating power, and conclusions drawn as to the presence of disease, the following extraneous factors must be considered and excluded: failure of absorption of the pheniodol from the alimentary tract; failure of the liver to secrete the pheniodol in the bile, which may occur in extensive liver disease, late pregnancy, or lactation (Olsson, 1943); failure of the gall-bladder to fill with the pheniodol-containing bile, owing to obstruction in the hepatic or cystic ducts, incompetence of the sphincter of Oddi, or stasis in the gall-bladder itself; premature emptying of the gall-bladder, which may occur in diabetes, according to Pendergrass and Hodes (1935); and, finally, technical factors such as faulty radiography or failure of the patient to take the pheniodol.

2. *Rate of filling.* This can be accurately assessed only after intravenous cholecystography, and so is not of great use in routine practice. According to Kerley (1950), if no shadow is visible in six hours after the administration of the contrast medium, disturbance of function of the liver or gall-bladder, or both, may be inferred. The average interval before the first appearance of the shadow is three to four hours. Ivy (1934) stated that the rate of concentration may be affected experimentally by autonomic impulses, being increased by sympathetic stimulation. This fact may have a bearing on the results obtained in patients in whom emotional factors play a part.

3. *Power of contractility and rate of emptying.* The demonstration of contraction in response to a fatty meal may not by itself be of much significance in determining the presence of gall-bladder disease, since contraction may be interfered with by extrinsic factors such as gastric or duodenal alkalinity, and conversely may be present even when the elasticity of the gall-bladder wall is impaired by disease. Study of the rate of emptying and proof of delay in emptying may be more useful (Kerley, 1950; Feldman, 1948). The normal emptying-rate, however, is variable, and it is difficult to decide where to draw the line between the normal and the abnormal. It is probable that an abnormality of function should not be presumed unless emptying fails to occur after six hours or more. Feldman (1948) went further, and did not regard an emptying-time of less than 36 hours as reliable evidence of disease. Finally it should

be remembered that most of the experimental work was done with tetraiodophenolphthalein, and it seems likely that pheniodol may itself delay the rate of emptying (Copleman, 1946).

4. *Visualization of ducts.* Copleman (1946) regarded good visualization of the cystic and common bile-ducts as valuable confirmation of a normal function of the gall-bladder and sphincter of Oddi. On the other hand, Feldman (1948) considered that clear visualization of the bile-ducts suggests poor tone in the sphincter. Visualization of the hepatic duct is said to be an indication of spasm of the sphincter of Oddi.

II. *The significance of the results of cholecystography in terms of gall-bladder disease*

The diagnosis of gall-bladder disease from the results of cholecystography is mainly a matter of inference from a demonstrable disorder of function, except where the radiological demonstration of gall-stones provides unequivocal evidence of disease. In the present state of our knowledge reliance must be placed almost solely on the demonstration of normal or faulty concentrating power, as shown by the presence or absence of visualization. In analysing the results of cholecystography it is proposed as far as possible to employ a uniform classification involving four groups:

Group I. Cases in which there was no radiological evidence of gall-stones and the shadow of the gall-bladder was considered to be of adequate intensity. Sub-group *Ia* includes cases in which there was no abnormality of contractility or gross anatomical abnormality. Sub-group *Ib* includes cases in which there was gross anatomical abnormality or failure of contractility.

Group II. Cases in which there was no radiological evidence of gall-stones, but in which visualization, though present, was doubtful or of inadequate intensity.

Group III. Cases in which there was no radiological evidence of gall-stones, but in which no visualization occurred.

Group IV. All cases showing radiological evidence of gall-stones, either opaque or non-opaque. Sub-group *IVa* includes cases in which visualization was adequate, as in Group I, sub-group *IVb* cases in which it was doubtful or inadequate, as in Group II, and sub-group *IVc* those in which no visualization occurred, as in Group III.

The question of what constitutes adequate visualization is one on which there is little agreement, but in the present series an attempt has been made to draw an objective boundary, by including all cases in which the gall-bladder shadow was as dense as, or more dense than, the vertebral transverse processes, in Groups I and *IVa*, and cases in which it was less dense in Groups II and *IVb*. This definition leads to a classification of more shadows as faint or doubtful than most authors would allow, and this fact is reflected in the percentages given in Table VIII, which shows the incidence of the four groups in a consecutive series of unselected cholecystograms. The interpretation of these results in terms of disease must depend upon a knowledge of two variable factors, first

the degree to which the gall-bladder can carry on its normal functions in the presence of disease, and secondly the delicacy of cholecystography as an indication of abnormal or deficient function. Theoretical considerations are not of great value in answering these questions, though a knowledge of the anatomical and physiological changes in the various diseases may help in confirming the conclusions reached by more empirical methods. The method employed in the

TABLE VIII
Results in a Series of 400 Unselected Cholecystograms

	Definition	Number of cases
Group I	Cholecystograms with shadow of normal intensity, with no evidence of gall-stones	257 (64%)
Sub-group Ia	Without anatomical abnormality or failure of contractility	199 (50%)
Sub-group Ib*	With either anatomical abnormality or failure of contractility	58 (14%)
Group II	Cholecystograms with shadow of poor intensity, with no evidence of gall-stones	21 (5%)
Group III	Cholecystograms with no gall-bladder shadow and no evidence of gall-stones	47 (12%)
Group IV	Cholecystograms with radiological evidence of gall-stones	75 (19%)
Sub-group IVa	Gall-bladder shadow of normal intensity	31 (8%)
Sub-group IVb	Gall-bladder shadow of poor intensity	20 (5%)
Sub-group IVc	No gall-bladder shadow	24 (6%)
* Further analysis of sub-group Ib gave the following results:		
	Failure of contractility	47
	Irregularity of outline	7
	Transverse septum	4
	Angulation of gall-bladder	1
	Left-sided gall-bladder	1
	Gall-bladder visible in straight film	1

present investigation is that of comparison between the cholecystographic findings and the pathological condition revealed by examination of the gall-bladder at operation and *post mortem*. General inferences from a series of this nature, including only cases in which pathological confirmation is forthcoming, are open to serious objection for the following reasons. Since disease of the gall-bladder is seldom fatal, reliance has to be placed chiefly on the results of operation, and cholecystograms of patients who ultimately come to operation are far from being an unselected series. They are biased heavily in favour of the abnormal cases, since the surgeon naturally does not operate when he believes the gall-bladder to be normal. This consideration applies specially to series in which the cholecystographic results obtained in a number of patients submitted to cholecystectomy are analysed. It is less evident, though still pertinent, when the findings at operation are analysed in a given series of cholecystograms. The present series consists of 90 cases, and combines the two methods. Two hundred unselected cases were followed up, and the pathological conditions found at operation noted in 28 cases; the other 62 consist of patients known to have undergone operation for gall-bladder disease and to have had previous

TABLE IX

Series of 90 Cholecystograms of Patients Subsequently Operated on: Correlation of Results with Pathological Findings

	Number of cases
Group I 'Normal gall-bladder function.' (Shadow of normal intensity without radiological evidence of gall-stones):	19 (21%)
<i>Gall-bladder normal</i>	13 (68%)
<i>Simple chronic cholecystitis</i>	4 (21%)
<i>Gall-stones present</i> (gall-bladder normal, 1; chronic cholecystitis, 1)	2 (11%)
Sub-group Ia (Without anatomical abnormality or failure of contractility):	14 (74%)
<i>Gall-bladder normal</i> (duodenal ulcer, 3; appendicitis, 2; gastric ulcer, benign polyp of stomach, carcinoma of stomach, diverticulum of caecum, ovarian tumour, 1 each; nothing abnormal found, 2)	12 (86%)
<i>Simple chronic cholecystitis</i>	2 (14%)
Sub-group Ib (With either anatomical abnormality or failure of contractility):	5 (26%)
1. Irregularity and lack of definition of outline.	1
<i>Gall-bladder normal</i>	1
2. Irregularity of outline and failure of contractility. <i>Gall-stones with chronic cholecystitis</i>	1
3. Irregularity of outline only. <i>Simple chronic cholecystitis</i>	1
4. Lack of definition of outline and angulation. <i>Simple chronic cholecystitis</i>	1
5. Failure of contractility only. <i>Gall-stones with normal gall-bladder</i>	1
Group II 'Doubtful gall-bladder function.' (Shadow of poor intensity without radiological evidence of gall-stones):	7 (8%)
<i>Simple chronic cholecystitis</i>	2 (29%)
<i>Gall-stones present</i> (with acute cholecystitis, 1; with empyema, 1; with chronic cholecystitis, 2)	4 (57%)
<i>Carcinoma of gall-bladder</i>	1 (14%)
Group III 'Abnormal gall-bladder function.' (No shadow obtained; no radiological evidence of gall-stones):	24 (27%)
<i>Gall-bladder normal</i> (enlarged glands found at porta hepatis)	1 (4%)
<i>Simple chronic cholecystitis</i>	1 (4%)
<i>Gall-stones</i> (with empyema, 2; with chronic cholecystitis, 20)	22 (92%)
Group IV 'Gall-stones visible' (opaque or non-opaque):	40 (44%)
<i>Gall-bladder normal</i>	1 (2.5%)
<i>Gall-stones present</i>	39 (97.5%)
Sub-group IVa (Shadow of normal intensity):	11 (27%)
<i>Gall-stones present</i> (with normal gall-bladder, 4; with cholesterolosis, 1; with chronic cholecystitis, 6)	11 (100%)
Sub-group IVb (Shadow of poor intensity):	10 (25%)
<i>Gall-bladder normal</i> (chronic pancreatitis)	1 (10%)
<i>Gall-stones present</i> (with gangrenous cholecystitis, 1; with chronic cholecystitis, 8)	9 (90%)
Sub-group IVc (No shadow obtained):	19 (48%)
<i>Gall-stones present with chronic cholecystitis</i>	19 (100%)

cholecystograms (Table IX). To supplement this evidence an attempt has been made to aggregate the results of this and other similar series found in the literature, and from the combined figures to assess the significance of the findings obtained by cholecystography (Table X).

TABLE X
Analysis of Results and Pathological Findings in Various Series of Cholecystograms

1. SERIES ANALYSED

(T.I.P.: tetraiodophenolphthalein. P.I.: pheniodol.)

<i>Authors and contrast medium</i>	<i>Number of cases</i>	<i>Group I</i>	<i>Group II</i>	<i>Group III</i>	<i>Group IV</i>
Kirklin (1931) . . .	726	287 (39%)	39 (5%)	106 (15%)	294 (41%)
Oral T.I.P.					
Ferguson and Palmer (1933) .	169	9 (5%)	12 (7%)	90 (53%)	58 (34%)
Intravenous T.I.P.					
Hardman (1937) . . .	184	28 (15%)	37 (20%)	71 (39%)	48 (26%)
Oral T.I.P.					
Levyn and Meyers (1940) . .	54	16 (30%)	11 (20%)	9 (17%)	18 (33%)
Oral T.I.P.					
Jarvis and Cayer (1947) . .	80	4 (5%)	5 (6%)	25 (31%)	46 (58%)
Oral P.I.					
Morales and Swedberg (1949) .	545	15 (3%)	38 (7%)	303 (55%)	189 (35%)
Oral T.I.P. and P.I.					
Present series . . .	90	19 (21%)	7 (8%)	24 (27%)	40 (44%)
Total . . .	1,848	378 (21%)	149 (8%)	628 (33%)	693 (38%)

2. PATHOLOGICAL FINDINGS

	<i>Number of cases</i>	<i>Normal gall-bladder</i>	<i>Cholesterolemia or cholecystitis alone</i>	<i>Gall-stones</i>	<i>Miscellaneous</i>
Group I: 'Normal gall-bladder function' (shadow of normal intensity without radiological evidence of gall-stones):					
Kirklin . . .	287	257 (90%)	24 (8.5%)	4 (1%)	2 (0.5%)
Ferguson and Palmer .	9	6 (67%)	1 (11%)	2 (22%)	..
Hardman . . .	28	21 (75%)	3 (11%)	4 (14%)	..
Levyn and Meyers .	16	10 (63%)	2 (12%)	4 (25%)	..
Jarvis and Cayer .	4	1 (25%)	3 (75%)
Morales and Swedberg .	15	4 (27%)	8 (53%)	3 (20%)	..
Present series . .	19	13 (68%)	4 (21%)	2 (11%)	..
Total . . .	378	312 (83%)	45 (11.5%)	19 (5%)	2 (0.5%)
Group II: 'Doubtful gall-bladder function' (shadow of poor intensity without radiological evidence of gall-stones):					
Kirklin . . .	39	2 (5%)	8 (20.5%)	28 (72%)	1 (2.5%)
Ferguson and Palmer .	12	5 (42%)	2 (16%)	5 (42%)	..
Hardman . . .	37	8 (21.5%)	15 (40.5%)	14 (38%)	..
Levyn and Meyers .	11	3 (27.5%)	1 (9%)	7 (63.5%)	..
Jarvis and Cayer .	5	..	2 (40%)	3 (60%)	..
Morales and Swedberg .	38	2 (5.5%)	6 (16%)	29 (76%)	1 (2.5%)
Present series . .	7	..	2 (29%)	4 (57%)	1 (14%)
Total . . .	149	20 (13.5%)	36 (24%)	90 (60.5%)	3 (2%)

	<i>Number of cases</i>	<i>Normal gall- bladder</i>	<i>Cholestero- losis or cholecysti- tis alone</i>	<i>Gall- stones</i>	<i>Miscel- laneous</i>
Group III: 'Abnormal gall-bladder function' (no shadow obtained, and no radiological evidence of gall-stones):					
Kirklin	106	3 (3%)	9 (8.5%)	90 (85%)	4 (3.5%)
Ferguson and Palmer .	90	9 (10%)	6 (7%)	71 (79%)	4 (4%)
Hardman . . .	71	10 (14%)	20 (28%)	41 (58%)	..
Levyn and Meyers . .	9	4 (45%)	1 (10%)	4 (45%)	..
Jarvis and Cayer . .	25	..	2 (8%)	22 (88%)	1 (4%)
Morales and Swedberg .	303	12 (4%)	33 (11%)	254 (84%)	4 (1%)
Present series . . .	24	1 (4%)	1 (4%)	22 (92%)	..
Total	628	39 (6%)	72 (11.5%)	504 (80.5%)	13 (2%)
Group IV: 'Gall-stones visible' (opaque or non-opaque):					
Kirklin	294	292 (99%)	2 (1%)
Ferguson and Palmer .	58	1 (2%)	..	57 (98%)	..
Hardman . . .	48	2 (4%)	..	46 (96%)	..
Levyn and Meyers . .	18	18 (100%)	..
Jarvis and Cayer . .	46	..	3 (6%)	43 (94%)	..
Morales and Swedberg .	189	7 (3.5%)	..	181 (96%)	1 (0.5%)
Present series . . .	40	1 (2.5%)	..	39 (97.5%)	..
Total	693	11 (1.5%)	3 (0.5%)	676 (97.5%)	3 (0.5%)

**CHARACTER OF SHADOW WHEN GALL-STONES WERE DIAGNOSED
RADIOLOGICALLY**

	<i>Number of cases</i>	<i>Group IVa Good shadow</i>	<i>Group IVb Poor shadow</i>	<i>Group IVc No shadow</i>
Kirklin (1931)	294	124 (42%)	78 (26.5%)	92 (31.5%)
Levyn and Meyers (1940) .	18	5 (28%)	5 (28%)	8 (44%)
Doran, Lewis, Hanssen, Spier, and Doran (1941) . . .	45	29 (64%)	..	16 (36%)
Jarvis and Cayer (1947) . .	46	11 (24%)	27 (59%)	8 (17%)
Morales and Swedberg (1949) .	189	62 (33%)	62 (33%)	65 (34%)
Present series	67	13 (19.5%)	13 (19.5%)	41 (61%)
Total	659	244 (37%)	185 (28%)	230 (35%)

Reference to Table X shows that patients whose cholecystograms fall into Group I, and whose gall-bladders were regarded as showing normal function, were proved to have a normal gall-bladder in 83 per cent. of cases, and that 17 per cent. showed disease of the gall-bladder. Of the latter class two-thirds had cholecystitis or cholesterosis without gall-stones, and nearly one-third had gall-stones. A study of the figures quoted reveals that in most of the series the number of cases analysed is small, and agreement between the percentages showing normal or diseased gall-bladders is not good. The disagreement reflects the limitations inherent in this method of study; the larger the series, the more nearly are the results likely to reflect the true state of affairs. An attempt was made in the present series to separate the cases in which there was some anatomical abnormality present (Group Ib). Though the number of cases was too small to be of great significance, the result seems to suggest that the presence of such features as angulation or constriction of the gall-bladder and irregularity of outline increases the likelihood of disease, and conversely that the presence of a gall-bladder shadow that is smooth, regular, and of normal shape

decreases its likelihood. Such abnormalities must, however, be fairly gross, and minor irregularities are probably of no significance. In the other series reviewed this possibility has not been investigated, but it receives some support from the results obtained by Royer and Richer (1947) as regards the appearances in cholecystitis, which are referred to below. Most authorities, on the other hand, regard such abnormalities as of little significance. There is reason to think that the proportion of normal gall-bladders in Group I is too low, but nevertheless it is probable on theoretical grounds that an appreciable number of gall-bladders in this group will prove to be diseased in spite of apparently normal function as shown by cholecystography; in this the gall-bladder is probably analogous to other organs such as the heart, liver, and kidneys, whose reserve power enables them to maintain apparently unimpaired function even in the presence of extensive disease. The impression that a normal cholecystogram necessarily excludes biliary-tract disease, as suggested by Graham, Cole, Copher, and Moore (1928), is not correct.

Cases falling in Group II, in which the function of the gall-bladder was regarded as slightly impaired, are shown in Table X to include a large proportion of patients who had disease of the gall-bladder (86 per cent.), including 60.5 per cent. who had gall-stones, and 24 per cent. who had simple cholecystitis or cholesterolosis. In the present series all the patients in this group had a diseased gall-bladder. There is fair agreement between the percentages in the various series. Such a result is opposed to the general view of the significance of this type of result. Newell (1948) regarded a faint shadow as most uncertain evidence of disease; Smith (1944) stated that only 60 per cent. of such patients are likely to have disease, and Feldman (1948) that a small percentage of gall-bladders giving a faint shadow are abnormal. The presence of anatomical abnormalities or failure of contractility cannot be determined accurately where the shadow is of poor intensity, and is therefore not very helpful. Of cases falling into Group III, 96 per cent. in the present series and 94 per cent. in the aggregate series showed evidence of disease. Gall-stones were present in 80.5 per cent., simple cholecystitis in 11.5 per cent., and miscellaneous conditions, including tumours of the gall-bladder, in 2 per cent. In the present series the figures are similar; in the single case in which the gall-bladder was found to be normal a possible cause for the failure of visualization was present, namely, enlarged glands at the porta hepatis, which were thought to account for the patient's jaundice by pressure on the hepatic duct, and could in this way have prevented access of pheniodol to the gall-bladder. Factors outside the gall-bladder which may prevent visualization have been mentioned already, and, provided that they are kept in mind, errors due to them are likely to be few. In the remaining cases in this group in which the gall-bladder was normal, the absence of a shadow was due to severe hepatic disease or to obstruction in the hepatic or cystic ducts. Such conditions will either be indicated by the clinical picture or imply the existence of gall-stones, biliary sand, or tumours of the bile-ducts, requiring treatment analogous to that of gall-bladder disease. In cases falling in Group IV, in which gall-stones are directly demonstrated,

accuracy should be complete, but occasionally, as shown by the figures quoted, gall-stones are reported to be present when they are absent.

The present writer has no personal experience from which to assess the significance of failure of contractility, or delay in filling and emptying of the gall-bladder, in terms of disease. Opinion seems to be divided on the subject. Newell (1948) regarded persistence of the gall-bladder shadow as of no diagnostic value. Kerley (1950) and Feldman (1948) both regarded it as of limited value as an indication of cholecystitis, with or without gall-stones, cystic-duct obstruction, or biliary dyskinesia. It seems that its chief value may be in indicating biliary dyskinesia, except when this condition has resulted in poor or absent visualization. Similar conclusions may apply to visualization of the ducts, the chief use of which is probably to confirm the normality of the gall-bladder when this is suggested by other evidence.

III. Cholecystographic findings in various diseases of the liver and gall-bladder

It may throw further light on the problem with which this paper is concerned if the results obtained in various diseases of the liver and gall-bladder are compared with the pathological changes. An analysis of the cholecystographic results obtained in the present series and by other authors in such diseases, and in cases where the gall-bladder was found to be normal, is given in Table XI.

Cholecystitis. In the majority of cases of cholecystitis gall-stones are present. MacCarty (1919), in a series of 365 cases, stated that stones were present in 69 per cent. of cases of acute inflammation, 76 per cent. of cases of chronic catarrhal cholecystitis, and 93 per cent. of cases of advanced chronic cholecystitis with fibrosis and scarring. Acute cholecystitis results in thickening of the wall of the gall-bladder from oedema, congestion of the serous surface, and infiltration with leucocytes which are often lymphocytic rather than polymorphonuclear. The epithelium, according to Graham, Cole, Copher, and Moore (1928), is often surprisingly well preserved. Ivy (1934) stated that acute inflammation, especially if present mainly in the deeper layers of the gall-bladder wall, does not at first decrease the power of concentration, but will do so if it persists. Experimentally, acute cholecystitis in dogs may or may not prevent absorption, according to the site and extent of the lesion. Restoration of the absorptive function may occur after recovery from acute inflammatory episodes. Chronic cholecystitis shows changes at first approximating to those of the acute stage, but later granulation tissue becomes more abundant in the submucosa and results in the replacement of muscular and elastic tissue by fibrous tissue; the epithelium is destroyed and the villi are debased or absent, often with ulceration. In the final stages the gall-bladder is left as an inert bag either with a thickened and contracted wall or, if obstruction to the cystic duct occurs, with considerable dilatation and thinning. It was stated by Newman (1933) that cholecystitis leads to a loss of the power of selective absorption, bile-salts being absorbed with the other constituents of the bile, and as a result the cholesterol becomes less soluble and is precipitated in the form of calculi.

TABLE XI

1. Effect of Gall-bladder Disease, with and without Gall-stones, on Visualization
Compiled from Hardman (1937), Jarvis and Cayer (1947), Morales and Swedberg (1949), and the present series

	Number of cases	Good shadow	Poor shadow	No shadow
<i>Gall-stones present:</i>				
Gall-bladder normal	205	50 (24%)	37 (18%)	118 (58%)
Acute cholecystitis	97	5 (5%)	14 (15%)	78 (80%)
Chronic cholecystitis	341	29 (8.5%)	85 (25%)	227 (66.5%)
Cholesterolosis	17	8 (47%)	3 (18%)	6 (35%)
Total	660	92 (14%)	139 (21%)	429 (65%)
<i>Gall-stones absent:</i>				
Acute cholecystitis	8	1 (12.5%)	2 (25%)	5 (62.5%)
Chronic cholecystitis	87	15 (17%)	23 (26%)	49 (57%)
Cholesterolosis	15	4 (27%)	4 (27%)	7 (46%)
Total	110	20 (18%)	29 (26.5%)	61 (55.5%)

2. Results of Cholecystography in Various Diseases

	Number of cases	Group I	Group II	Group III	Group IV
<i>Simple chronic cholecystitis (without gall-stones):</i>					
Kirklin (1931)	41	24 (57.5%)	8 (20%)	9 (22.5%)	..
Ferguson and Palmer (1933)	9	1 (11%)	2 (22%)	6 (67%)	..
Hardman (1937)	37	3 (8%)	15 (41%)	19 (51%)	..
Adams and Stranahan (1947)	26	7 (27%)	..	19 (73%)	..
Jarvis and Cayer (1947)	5	2 (40%)	1 (20%)	1 (20%)	1 (20%)
Royer and Richer (1947)	144	87 (60%)	43 (30%)	14 (10%)	..
Morales and Swedberg (1949)	38	6 (16%)	4 (10.5%)	28 (73.5%)	..
Present series	7	4 (57%)	2 (29%)	1 (14%)	..
Total	307	134 (43%)	75 (25%)	97 (31.5%)	1 (0.5%)
<i>Cholelithiasis:</i>					
Kirklin (1931)	414	4 (1%)	28 (7%)	90 (22%)	292 (70%)
Ferguson and Palmer (1933)	135	2 (1.5%)	5 (4%)	71 (52.5%)	57 (42%)
Hardman (1937)	105	4 (4%)	14 (13%)	41 (39%)	46 (44%)
Levyn and Meyers (1940)	33	4 (12%)	7 (21%)	4 (12%)	18 (55%)
Doran, Lewis, Hanssen, Spier, and Doran (1941)	217	26 (12%)	19 (9%)	129 (59%)	43 (20%)
Adams and Stranahan (1947)	753	5 (1%)	..	197 (26%)	551 (73%)
Jarvis and Cayer (1947)	68	..	3 (4%)	22 (33%)	43 (63%)
Morales and Swedberg (1949)	468	3 (1%)	29 (6%)	264 (54%)	182 (39%)
Present series	67	2 (3%)	4 (6%)	22 (33%)	39 (58%)
Total	2,260	50 (2%)	109 (5%)	830 (37%)	1,271 (56%)
<i>Infective hepatitis:</i>					
Rudisill (1930)	8	7	..	1	..
Huber (1944)	10	7	3
Hrdlicka, Watkins, and Robb (1945)	4	2	1	1	..
Readinger, Swift, Gardner, and Sheedy (1950)	43	26	8	9	..
Total	65	42 (65%)	12 (18%)	11 (17%)	..

	<i>Number of cases</i>	<i>Group I</i>	<i>Group II</i>	<i>Group III</i>	<i>Group IV</i>
<i>Gall-bladder found to be normal at operation:</i>					
Kirklin (1931)	262	257 (98%)	2 (1%)	3 (1%)	..
Ferguson and Palmer (1933)	21	6 (28%)	5 (24%)	9 (43%)	1 (5%)
Hardman (1937)	35	21 (60%)	6 (17%)	6 (17%)	2 (6%)
Levyn and Meyers (1940)	17	10 (59%)	3 (17.5%)	4 (23.5%)	..
Morales and Swedberg (1949)	25	4 (16%)	2 (8%)	12 (48%)	7 (28%)
Present series	15	13 (87%)	..	1 (6.5%)	1 (6.5%)
Total	375	311 (83%)	18 (5%)	35 (9%)	11 (3%)

Caylor and Bollman (1927) stated that concentrating power in acute and chronic cholecystitis, though usually lost, may occasionally be increased when the mucosa is hypertrophic and rugose. Examination of the results in Table XI shows that visualization can and does occur in both acute and chronic cholecystitis. Other authors agree on the whole that visualization can occur in a large number of cases of chronic cholecystitis without gall-stones, and that its occurrence depends on the extent of the damage to the mucosa. In acute cholecystitis Kerley (1950) maintained that visualization never occurs, but this statement seems to be rather too sweeping. Certain other signs have been adduced as evidence of cholecystitis; Royer and Richer (1947), reviewing the results of cholecystography in a series of 144 cases of cholecystitis without gall-stones, found ill-defined outlines in 23 per cent., deformity (either curvature or angulation) in 21 per cent., and delay in emptying in 16 per cent. Delay in filling and emptying was also stated to be characteristic of cholecystitis by Feldman (1948).

Cholesterolemia. There is considerable controversy as to the aetiology of this condition, and as to whether it can occur in a gall-bladder which is otherwise normal in structure and function, or whether, as Newman (1933) suggested, it always indicates a mild degree of cholecystitis. Hypercholesterolemia is probably a predisposing factor, possibly combined with obstruction to the lymphatic drainage. Pathologically, cholesterol is found in the epithelial cells of the mucosa, in tissue histiocytes, and scattered free in the stroma. It is recognized that evidence of normal gall-bladder function on cholecystography is not uncommon in this condition. Feldman (1948) described rapid emptying and marked contractility, but other observers such as Kerley (1950) have regarded delayed or 'fade-away' emptying (progressive diminution in the intensity of the shadow without reduction in its size) as more characteristic of the condition. Examination of Table XI shows that visualization occurred in 59 per cent. of cases, but was faint in 22 per cent. Gall-stones were often present.

Cholelithiasis. The presence of gall-stones may be established by direct demonstration, or indirectly by interference with gall-bladder function due to an associated cholecystitis, to obstruction to the cystic duct, or to stasis resulting from blockage of the common bile-duct. Gall-stones may be present without infection, usually either as a solitary cholesterol stone or as multiple pigment stones: and these may not be associated with cholecystitis unless there is

obstruction to the cystic duct or in the neck of the gall-bladder. The inflammatory types of stone are multiple, and contain mixed calcium and cholesterol. They are always associated with cholecystitis, which is usually chronic, but may be an acute exacerbation. Visualization may therefore occur in the presence of gall-stones, and in Table XI it is recorded in 35 per cent. of cases, though faint in 21 per cent. Most authors agree that if visualization occurs gall-stones are usually directly demonstrable, either as opaque shadows of characteristic shape and texture, or as non-opaque defects within the shadow of the gall-bladder. The number of cases in which gall-stones were present but unsuspected in a normally visualized gall-bladder is small (2 per cent.). A large proportion of the cases in which no visualization occurred, however, failed to show direct evidence of gall-stones (79 per cent. in the series reviewed), and it is therefore clear, as Jarvis and Cayer (1947) pointed out, that the accuracy of the radiological diagnosis of gall-stones is much greater in the presence of normal gall-bladder function. The combination of gall-stones and cholecystitis, as would be expected, reduces the proportion of cases showing visualization below that occurring when either condition occurs alone.

Tumours of the gall-bladder. Benign tumours of the gall-bladder do not normally interfere with visualization, as was shown by Kirklin (1935). They may be confused with non-opaque gall-stones, since they can appear as rounded filling defects in the gall-bladder shadow. Carcinomata, on the other hand, usually prevent visualization; the reasons for this are, first that they are often infiltrating growths resembling scirrhous carcinomata of the alimentary canal, and so interfere with the absorptive function by destroying the mucosa or by blocking the lymphatic channels; secondly that they almost always, sooner or later, cause obstruction to the cystic duct; and thirdly that there is a proved association between carcinoma of the gall-bladder and chronic cholecystitis or gall-stones. A few cases have been described in which visualization has occurred; Kirklin (1935) described two such cases out of 16 cases of carcinoma, and in one of these gall-stones were also present. Nevertheless, apparent filling defects, unless very constant on repeated examination, should be accepted as evidence of neoplasm only with great reserve, as they are usually due to other conditions, and can occur in normal gall-bladders.

Biliary dyskinesia. This term is used to describe functional disorders of the gall-bladder and bile-ducts mainly affecting motility, and capable of giving rise to pain, nausea, anorexia, and other symptoms. Such a disorder may be difficult to distinguish from organic disease. Although functional disorder of the biliary system is often invoked unjustifiably to explain obscure dyspepsia for which no other cause can be found, there is much experimental and pathological evidence that it exists. This evidence has been well reviewed by Newman (1933) and Ivy (1947). If functional disorders of the musculature of the biliary system can give rise to symptoms, it is obviously important that they should be diagnosed, or at least not confused with gall-stones or other organic disease requiring surgical treatment. Can radiology help in this problem? Newman (1933) described the results of cholecystography in the spastic and atonic types

as follows. In the spastic form the gall-bladder gives a shadow of average or slightly increased density, normal in size but well filled, contracting only slightly after a fatty meal, and showing a delayed emptying-time; the ducts, if visualized, appear dilated. The stomach when examined with a barium meal is of the small horizontal type, emptying either rapidly or with delay due to pylorospasm. In the atonic form the gall-bladder tends to be poorly visualized, and is long and thin in shape; there is little contraction after a fatty meal, and emptying is delayed. Ivy (1947) was sceptical as to the reliability of radiological evidence of biliary dyskinesia, chiefly on the grounds that the normal emptying-time is very variable, and that minor differences in the size and shape of the gall-bladder, or of the cystic and common bile-ducts, are apt to occur in patients who show little evidence of dyskinesia. In conclusion, it appears that at the present time cholecystography can do little more than suggest the possible presence of such a condition, leaving the burden of proof on the clinical symptoms and signs and on the response to appropriate treatment. In view of the known liability of stasis in the gall-bladder to prevent visualization, it is not even possible to assert with confidence that non-visualization is evidence of organic rather than functional disease.

Extra-biliary conditions. 1. *Hepatic disease.* Cholecystography is not necessarily contra-indicated. Pheniodol is rapidly excreted by the kidneys, and will not accumulate even if the liver fails to secrete it. In toxic or infective jaundice visualization occurs in the majority of cases (Table XI). Readinger, Swift, Gardner, and Sheedy (1950) stated that a normal shadow is obtained in 90 per cent. of cases in which the serum-bilirubin is below 11 mg. per 100 ml. (normal 0.2 mg. per 100 ml.), but that if the figure rises above this level no shadow will be obtained.

2. *Pregnancy.* Stasis is said to occur during the last trimester, and to be responsible for failure of visualization, which at this period should be regarded with considerable reserve as evidence of gall-bladder disease.

3. *Other conditions.* Several conditions such as sprue, pernicious anaemia, thyroid abnormalities, peptic ulcer, pulmonary tuberculosis, and diabetes have been held responsible for failure of visualization at various times. Good and Kirklin (1937), however, reviewed the results of cholecystography in a large number of such conditions, and concluded that the presence of a generalized disease *per se* has no effect on gall-bladder function, but that such factors as dyskinesia due to reflex contraction or paresis of the gall-bladder wall, leading to stasis and undue rapidity of filling and emptying, may in such cases be responsible for negative cholecystographic results.

Of the cases in which the gall-bladder was proved at operation to be normal, the percentage showing evidence of abnormality on cholecystography was 17 in the aggregate series and 13 in the present series. In the aggregate series 5 per cent. of such cases gave a faint shadow, 9 per cent. no visualization, and 3 per cent. radiological evidence of gall-stones. For reasons already discussed it is likely that these percentages are too high, since large numbers of patients whose cholecystograms are normal never come to operation, and such cholecystograms

must include a smaller percentage of diseased gall-bladders than those of patients who undergo operation. Nevertheless the fact remains that some cholecystograms show evidence of defective function, although no actual disease can be detected at operation. It is probable that faulty technique accounts for a number of such cases, but there is no doubt that they occur even with the most meticulous technique, and in these cases such factors as Good and Kirklin (1937) described are probably responsible.

Conclusions

Provided that the technique is strictly controlled, the presence of disease of the gall-bladder can be inferred with a fairly high degree of certainty if there is complete failure of visualization; the likelihood that disease will be present in such cases is of the order of 20 to one. If faint visualization is present the likelihood is not so high, and is of the order of six to one. If gall-stones are demonstrated directly, either as positive or negative shadows, the likelihood of disease is naturally much greater, though even then errors occur. The absence of disease in cases in which the cholecystogram is normal is not so certain, and the likelihood in this case is of the order of five to one. These results are in conformity with the nature of the investigation, which is primarily a test of function rather than a demonstration of morbid anatomy, and emphasize the need of interpreting cholecystograms in conjunction with the rest of the clinical and pathological evidence. In reporting, results should therefore be expressed in terms of function rather than of disease, except when direct evidence of gall-stones is obtained. The diagnosis of disease should rest on assessment of all the evidence available, and is therefore not strictly the province of the radiologist, although he may be of considerable assistance in virtue of his knowledge of the limitations of the examination, and of the degree to which disease of the gall-bladder interferes with, or is compatible with, normal function. It is clear from what has been said that our knowledge of normal gall-bladder function is far from complete, and that we know less about minor disturbances of function. It is in this field that the most fruitful advances are likely in making cholecystography a more reliable diagnostic tool. At present the radiological diagnosis of biliary dyskinesia is insufficiently reliable for practical use. Experimental investigation of the radiological features of disorders of motor function may, however, result in the emergence of valuable additional criteria, which can be used together with those derived from the concentrating power of the gall-bladder, and so make the test more delicate than it is at present. This can only be done with the help of reliable information as to the limits of the normal in such matters as the rate of filling, rate of emptying, and mode of emptying which may be sought on the lines suggested by the work of Boyden (1928), but by the use of the newer cholecystographic agents rather than tetraiodophenolphthalein. The development of an intravenous cholagogue analogous to cholecystokinin would also be of great assistance in this task.

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Summary

A series of 400 unselected cholecystograms has been reviewed, and certain aspects of the technique of cholecystography are examined. It is suggested that the practice of varying the dose of the contrast medium according to the patient's weight is advantageous, in spite of an increased liability to reactions with the larger doses. Diarrhoea after taking pheniodol is thought to be an infrequent cause of failure to absorb the contrast medium, and the reasons for this view are stated. The desirability of giving fat before the examination is discussed, and it is suggested that this step may be useful in conjunction with the double-dose technique, the results of which are reviewed.

A second series of 90 cases in which cholecystography has been followed by operation is analysed, and the correspondence between the results of radiology and the operative findings is studied. The figures are compared with several similar series in the literature, and an attempt is made, by aggregating the figures obtained, to formulate conclusions as to the probable significance of the results of cholecystography in terms of disease of the liver and gall-bladder, and as to the accuracy of the examination in the diagnosis of such conditions. It is concluded that the examination cannot give 100 per cent. accuracy, but that if it is used in combination with the clinical signs and symptoms, and with a knowledge of the probable implications of the results obtained, it may be of considerable value.

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BIOCHEMICAL AND PATHOLOGICAL STUDIES OF CONGENITAL PORPHYRIA¹

By J. E. KENCH, F. A. LANGLEY, AND J. F. WILKINSON

(From the Departments of Occupational Health, Obstetrics, and
Haematology, University of Manchester)

With Plate 21

IN recent years an increasing number of publications describing cases of acute porphyria has appeared, but cases of congenital porphyria are rare, and the literature concerning it is scanty. Recent investigations, both clinical and biochemical, have stressed the close relationship between the anomaly of porphyrin metabolism and increased haemolysis of circulating erythrocytes. Aldrich, Hawkinson, Grinstein, and Watson (1951) have described clinical improvement in a congenitally porphyric child after splenectomy. The level of porphyrin excretion was reduced, but did not fall to normal. Splenectomy was less successful in ameliorating symptoms in the patient of Gray and Neuberger (1952). Gray, Muir, and Neuberger (1950), in their studies with ¹⁵N-glycine, demonstrated a shortened life-span of the erythrocytes, and a much increased early formation of stercobilin; they regarded the latter as the most characteristic biochemical lesion in this disease. Interpretation of many data has been rendered difficult by lack of information as to the permeability to porphyrins of many natural membranes, such as those of the erythroblast or the red blood-corpuscle. The only observations regarding human placental permeability to porphyrins appear to be those of Woody (1949), who measured the porphyrin-content of urine and meconium in the newborn child of a mother who had acute intermittent porphyria. It is not possible to attach great significance to his figures, since the normal range of values for the meconium and urine of the newborn are not known, and this case was, moreover, complicated by the presence of the precursor porphobilinogen, and the possibility that the infant had inherited the acute porphyric trait. An opportunity to investigate the above aspects of porphyric metabolism occurred during the course of a study of a congenitally porphyric patient, M. S., who had already been described by Ashby (1926). The patient was delivered of a normal male child, and we were thus able, by measuring the concentration of porphyrins in maternal and neonatal blood and excreta, to conclude that the placenta was permeable to porphyrins, as also was the red-blood-corpuscular membrane, but that secretion into the breast milk did not occur. After the untimely death of our patient at the age of 27 years, post-mortem examination of the tissues showed widespread

¹ Received January 28, 1953.

evidence both of increased haemoglobin breakdown and of intermediary metabolism of porphyrin pigments. A preliminary note on the biochemical findings has been published (Kench and Papastamatis, 1952).

Experimental Methods and Results

A woman aged 25 years, who had congenital porphyria, was first studied by us in May 1947. She had remained in fairly good health since childhood, and had avoided much of the gross scarring due to photosensitization by the use of quinine ointments prescribed by Ashby. The patient was pregnant, and was

TABLE I
Blood Counts and Haemoglobin Concentration of the Congenital Porphyric Patient M. S. and of her Baby S.

Patient	Red blood-cells (millions per c.mm.)		Haemoglobin (gm. per 100 ml.)		Colour index		Reticulocytes (%)	
	Highest value	Lowest value	Highest value	Lowest value	Highest value	Lowest value	Highest value	Lowest value
M. S.	2.92	2.19	9.2	7.4	1.27	1.03	16.2	6.1
Mean	2.61		8.5		1.11		10.0	
(No. of observations)	(15)		(15)		(15)		(16)	
Baby S.	5.97	4.68	21.9	15.4	1.28	0.96	6.0	0.8

TABLE II
Urobilinogen Excretion of the Congenital Porphyric Patient M. S.

Material examined	Urobilinogen (mg. per day)		
	Highest value	Lowest value	Mean
Urine	99	0	47 (17 days)
Faeces	1,466	51	578 (11 observations)

delivered normally of a full-term male child on July 17, 1947. At that time there were considerable signs of increased breakdown of red blood-cells, namely, anaemia and reticulocytosis (Table I), nucleated red blood-cells, and normoblastic hyperplasia of the bone-marrow (July 22, 1947; we are indebted to Dr. M. C. G. Israëls for his kindness in examining the sternal-marrow biopsy and for his report). The detailed blood picture on July 28, 1947, was as follows: red blood-cells, 2,470,000 per c.mm.; haemoglobin, 8.3 gm. per 100 ml.; colour index, 1.17; reticulocytes, 15.4 per cent.; white blood-cells, 4,000 per c.mm.; (polymorphs, 67.5 per cent.; lymphocytes, 24 per cent.; mononuclears, 6 per cent.; eosinophils, 0.5 per cent.; basophils, 1.5 per cent.; metamyelocytes, 0.5 per cent.); nucleated red blood-cells, 1 per 200 white cells. The film showed pronounced anisocytosis and poikilocytosis, and platelets in moderate number. The serum-bilirubin (Malloy and Evelyn, 1937) on July 25 and July 30, 1947, was indirect-reacting, 0.5 mg. and 0.45 mg. per 100 ml. respectively. Urobilinogen excretion, measured by the method of Schwartz, Sborov, and Watson (1944), was much increased (Table II), as was observed by Gray, Muir, and Neuberger (1950) in their investigation. No porphobilinogen could be detected in any of several maternal urinary specimens examined (Watson, Schwartz, and Hawkinson, 1945), nor in the first urinary specimen (the only one tested) from the infant.

Porphyrins were extracted from separated red blood-corpuses and plasma by means of ethyl acetate and acetic acid (3:1 v/v), or by the usual ether-acetic-acid procedure. Ethyl-acetate or ether extracts were fractionated into hydrochloric acid, and subsequently the acid extracts were shaken with chloroform or treated with sodium hydroxide solution to separate deproto- and protoporphyrins by the usual procedures (Watson, 1937). Only coproporphyrin,

TABLE III
Porphyrins of Blood, Placenta, Urine, and Faeces of the Congenital Porphyric Patient M. S.

Date	Erythrocytes*	Plasma†	Whole blood	Placenta	Breast milk	Urine	Faeces
	($\mu\text{g}/100 \text{ ml.}$)	($\mu\text{g}/100 \text{ ml.}$)	($\mu\text{g}/100 \text{ ml.}$)	($\mu\text{g.}$)		(mg./day)	(mg./day)
23.5.47	70.0	88.5
24.5.47	41.6	..
25.5.47	42.8	..
17.7.47	544	774	612	692†	..		
22.7.47	262	31	109	..	(24.7.47) (25.7.47)		
25.7.47	295	59	136	..	0		
28.7.47	188	151	164		
30.7.47	388	126	225		
31.7.47	664	132	288		
1.8.47	526 (all C)	179	286		
2.8.47	100	233	193		
3.8.47	197 (C 84, U 113)	148	163		
4.8.47	188 (C 144, U 44)	95	124		
5.8.47	44 (all U)	29	34		
6.8.47	403 (C 330)	52	161		
7.8.47	582 (C 420, U 162)	77	279		
8.8.47	705 (C 361, U 345)	66	296		
Means	363	154	191		

* Erythrocytes contained coproporphyrin (C), mainly I, and uroporphyrin I (U), only; no deuteroporphyrin or protoporphyrin was detected.

† Only coproporphyrin found.

however, could be detected. Uroporphyrin was removed with ammonia from the extracted residue. The extract was adjusted to pH 3.1 and shaken with ethyl acetate to separate uroporphyrin III. In all instances total fluorescence remained in the aqueous phase, and it was concluded that only uroporphyrin I was present. All porphyrins were measured fluorimetrically (Rimington, 1943). Pooled coproporphyrin extracts of corpuscles and plasma were methylated and fractionated with cold, dry ether. Only traces of the more soluble coproporphyrin III were removed from the major insoluble fraction of coproporphyrin I. There was insufficient material for crystallization of the esters. Similar procedures were employed with the breast milk, and with the urine and faeces of mother and child (Tables III and IV). Qualitative analysis of the porphyrins of the meconium and of the maternal urine and faeces were made by the paper-chromatographic procedures of Nicholas and Rimington (1949) and Chu, Green, and Chu (1951) (Tables IV and V). The foetal blood at birth contained 256 $\mu\text{g.}$ and 306 $\mu\text{g.}$ of porphyrin per 100 ml. of red blood-cells and plasma respectively, the corresponding values in the mother being 544 $\mu\text{g.}$ and 774 $\mu\text{g.}$ per 100 ml. The newborn child was clinically normal, and no porphyrins could be detected in the blood on the sixth and subsequent post-natal days. No porphyrin was found in the breast milk. The meconium was very dark in colour, and contained 9.65 mg. of porphyrin, comprising approximately equal quantities of 8-, 6-, 4-,

Specimens
examined
qualita-
tively

3-, and 2-carboxylic porphyrins (Plate 21, Fig. 1). The baby's urine contained 140 µg. of porphyrin on the second day, but none could be detected in later specimens, nor in faeces collected after the third day.

TABLE IV
Porphyrins and Urobilinogen of Baby S.

Age (days)	Porphyrins					Urobilinogen	
	Erythrocytes (µg./100 ml.)	Plasma (µg./100 ml.)	Whole blood (µg./100 ml.)	Urine (µg./day)	Meconium (mg.)	Faeces	Urine (mg./day)
0	256	306	283	..	9.65
	uro copro 43* 213						46
2	140†	0.25
3	0	..	0‡	0.12
5	0	..	0	..
6	0	0	0	0	..
13	0	0	0	0
117	0

* Uroporphyrin I, insoluble in ethyl acetate at pH 3.1.

† All coproporphyrin.

‡ Some red ultraviolet fluorescence was present in the ether extract of this specimen, but was lost during storage.

Chromatographic analysis of meconium

Method	Number of COOH groups
Chu, Green, and Chu (1951)	$\begin{cases} 2+ \\ 3+ \\ 4 \quad \text{III}++ \\ \text{I}+++ \\ 8+++ \end{cases}$
Nicholas and Rimington (1949)	$\begin{cases} 2++ \\ 3+ \\ 4+++ \\ 6+++ \\ 8++++ \end{cases}$

TABLE V
Chromatograms of Porphyrins in Tissues and Excreta of the Congenital Porphyric Patient M. S.

Material examined	Porphyrins detected (number of COOH groups present)							
	1	2	3	4*	5	6	7	8
Urine		++++		+++	+		+	+++
Faeces	+	+++	+		++			
Liver		+	+		++		++	++
Spleen	?	+	+++		+	++	++	+++
Uterus	++			++	++	+	+	+++

* Chemical separation and chromatograms (Chu, Green, and Chu, 1951) showed the presence of both coproporphyrin isomers, I predominant in excreta, III in tissues other than blood. The relative concentrations of porphyrins were: Urine: coproporphyrin III: coproporphyrin I: uroporphyrin = 1:56:31; Faeces: coproporphyrin III: coproporphyrin I = 1:5.

Melting points of purified methyl esters: coproporphyrin III, 137–139° and 172°; coproporphyrin I, 249°; uroporphyrin I, 295°.

During a second pregnancy in 1949 the condition of the patient deteriorated rapidly, in spite of termination of pregnancy, and she died on August 22, 1949, with liver failure. The baby, a girl, was apparently normal at birth, but lived only for four days. Permission for post-mortem examination of the child was not given. Post-mortem examination of the maternal tissues revealed the presence of many porphyrin intermediates, as described by Nicholas and Rimington (1951) in meconium, liver, and faeces. Paper chromatography applied to the liver yielded discrete fluorescent spots corresponding to porphyrins containing eight, seven, six, four, three, and two carboxyl groups, while the spleen contained the complete series of 2- to 8-carboxylic porphyrins (Table V). Coproporphyrin-I methyl ester, with characteristic crystalline appearance and melting-point, was isolated from the maternal urine and faeces, while uroporphyrin I was similarly obtained from the meconium and from the maternal urine and liver (Plate 21, Fig. 2). Repeated chromatography of the methyl esters prepared from various tissues was performed on solid adsorbents, as described by Nicholas (1951), in attempts to isolate other porphyrin intermediates, but although microcrystalline products were obtained on three occasions there was insufficient material for further characterization.

Post-Mortem Findings in the Case of the Congenital Porphyric Patient, M. S.

Macroscopic examination. The body was that of a large woman, but the size of the body was great compared with the size of the hands and feet. The skin, especially of the hands and face, was of a brownish hue. The sclerae were yellowish-brown. The skin covering the anterior half of each leg was thickened and raised above the adjacent normal skin. There was considerable oedema of the legs and thighs. At the hilum of the lungs, and along the splenic vessels and round the abdominal aorta, the lymph-glands were moderately enlarged and red. *Bones and teeth.* The cortical bone of the femur, manubrium sterni, and jaw was red, but the cartilage retained its normal colour. Other bones were not examined. The last two molars of the left upper jaw were examined; both were red, and section of one showed that the coloration was confined to the dentine. In ultraviolet light both bone and teeth showed a red fluorescence in the stained areas. Greyish-pink marrow extended the whole length of the femur; the marrow in the manubrium was unusually fluid, and the adjacent bony cortex thin. The heart (400 gm.) was rather large, but corresponded to the weights of the other organs and the build of the patient. There was no significant abnormality, except that the myocardium was brownish and there were a few fine haemorrhages on the interventricular septum and left ventricular wall. The lungs (right 530 gm., left 480 gm.) showed passive congestion, and were moderately oedematous. The left pleural cavity was obliterated by fibrous adhesions. The peritoneum contained a very large quantity of straw-coloured fluid. The liver (1,680 gm.) showed a fairly coarse lobular cirrhosis (some lobules 1 cm. in diameter), the lobules being yellowish-brown and the intervening strands of fibrous tissue pink. There was cholesterolosis of the gall-bladder. The common bile-duct was patent. The pancreas was moderately enlarged. The spleen (1,020 gm.) was very much enlarged and firm, and the fibrous trabeculae were easily seen. The kidneys (right 210 gm., left 220 gm.) were pale and brownish, but otherwise normal. The bladder contained dark red urine. The appearances of the genitalia were those which follow a recent pregnancy. The brain (1,270 gm.) and other organs appeared normal.

Microscopic examination. Sections of most of the organs were stained with Mayer's haemalum and eosin and by the van Gieson technique. In addition relevant organs were stained for iron by the prussian-blue method, for melanin and uric acid by the methenamine-silver method with hydrogen-peroxide treated controls (Gomori, 1951), and with the Jenner-Giemsa stain. Unstained sections of bone, liver, and kidney were also examined by fluorescence-microscopy.

The *liver* showed the pattern of a typical coarse lobular (portal) cirrhosis; bile-duct proliferation was present, and the bands of fibrous tissue were lightly infiltrated with lymphocytes. A little iron-containing pigment, some intracellular and some extracellular, was present in the fibrous trabeculae. Brownish-green pigment was present in many parenchymal cells and in some Kupffer cells. This pigment could not be identified. It did not fluoresce, nor did it react to Gmelin's test, or show any well-defined colour-change when treated with hydrogen-peroxide tests which are positive for both bilirubin and porphyrin (Lillie, 1948). Tests for melanin were also negative. Although the *spleen* was enlarged, its general architecture was normal. There was a moderate increase in the amount of connective tissue present. Scanty or moderate quantities of free iron could be identified, often as fairly large compact deposits several microns in diameter, but sometimes more finely dispersed. The iron was both intracellular and extracellular, and was mostly present in the connective tissue, especially of the trabeculae. Many cells of the pulp contained pigment similar to that seen in the liver, but its nature could not be determined. In the *kidney* spherical green concretions were present in a few collecting tubules, and in the convoluted tubules greenish spherules could sometimes be seen. These concretions blackened when stained by the methenamine-silver method, probably owing to the presence of urates. Occasionally foci of lymphocytes, and small greenish spherules, one of which was surrounded by foreign-body giant cells, could be seen in the stroma. Some tubules contained eosinophilic casts, some of which gave a methenamine-silver reaction probably due to urates, and also a prussian-blue reaction. Sections of *skin* from the anterior abdominal wall and front of the leg were examined. In both there was in the deeper layers of the epidermis an unusually large amount of brown pigment, which gave a methenamine-silver reaction abolished by oxidation, and thus presumably was melanin. Round the sweat and sebaceous glands of the anterior abdominal wall there was a little lymphocytic infiltration. The skin from the front of the leg showed fibroblastic proliferation, a little lymphocytic infiltration, and scanty elastic tissue. The *bone-marrow* showed extensive myeloid hyperplasia, and no significant erythroid haemopoiesis. Megakaryocytes were conspicuous. No iron-containing or other pigment was found. *Bone* from the mid-shaft of the femur showed no histological abnormality, and although it gave a reddish fluorescence in ultraviolet light no pigment could be identified in granular form. Microscopic examination of a tooth showed no significant abnormality. The *lung* showed some normal areas, but in others the alveoli contained oedema fluid with occasional haemorrhages. Scattered throughout the oedematous areas were macrophages, many of which near blood-vessels contained iron pigment, suggesting that the haemorrhages were due to pulmonary hypertension. In places irregular hyaline plaques were plastered against the walls of the alveoli; these plaques were mingled with macrophages, but not with polymorphic leucocytes. The following organs were also examined microscopically, but no significant changes were found: uterus, ovary, heart, muscle, adrenal, pancreas, thyroid, pituitary, small intestine, stomach, and brain.

Discussion

The clinical picture of this patient, as present from birth and described by Ashby in 1926 when she was three years of age, comprised photosensitization, increased haemolysis, and red urine. The harmful and disfiguring effects of light had been ameliorated by the use of a quinine cream, and there was little scarring, but some thickening of the skin where it was exposed. Hirsutism was absent. Two molar teeth contained porphyrin deposited only in the dentine, the enamel being free of pigment, in contrast to the deciduous teeth of this patient, which according to Ashby's account were stained also in the enamel. At the time of her first pregnancy haemolytic anaemia of a severe grade had developed, and the bone-marrow was markedly hyperplastic. Two years later at post-mortem examination there was no significant evidence of erythroid haemopoiesis. Many organs contained extensive deposits of iron-containing pigments as well as porphyrins, and the continuous deposition of these pigments in the liver over a period of many years may have helped to initiate a cirrhotic process, but one cannot exclude the possibility that toxæmia may have contributed, with the factors of gross anaemia and the metabolic burden of pregnancy, to the fatal outcome.

The preponderance of porphyrins of type I configuration, observed in the blood and excreta of our patient, is a characteristic feature of congenital porphyria. The daily records of blood-porphyrin concentration, beginning at the term of her first pregnancy, showed values covering a wide range with varying proportions of coproporphyrin I and uroporphyrin I inside the corpuscles. Only coproporphyrin I could be detected in the plasma. Coproporphyrin I and uroporphyrin I, with much less coproporphyrin III, comprised the urinary porphyrins, while the faeces contained mainly coproporphyrin I, with less coproporphyrin III and protoporphyrin. Chromatography by the methods of Nicholas and Rimington (1949) and Chu, Green, and Chu (1951) demonstrated the presence of other urinary porphyrins containing seven and five carboxylic groups, while faecal porphyrins included 3- and 1-carboxylic porphyrins, but no detectable uroporphyrin. By application of chromatographic methods to the excreta of porphyric patients, Rimington and his colleagues have succeeded in isolating and characterizing several of these hitherto undescribed porphyrins (Rimington and Miles, 1951; MacGregor, Nicholas, and Rimington, 1952). Finally, the presence of many of these metabolic intermediates was demonstrated in maternal tissues, especially in the liver and spleen, although the quantities were too small to allow separation in a pure state. It is remarkable that the quantities of porphyrins present in the liver and kidneys were not evident by fluorescence-microscopy, although both bone and teeth showed marked red fluorescence in ultraviolet light (Borst and Königsdorffer, 1929). The baby showed a high blood-porphyrin concentration, with coproporphyrin and uroporphyrin I in the red cells but only coproporphyrin in the plasma. It was not possible to collect further specimens of blood from the infant until the sixth and 13th days, when no porphyrin could be detected. Before

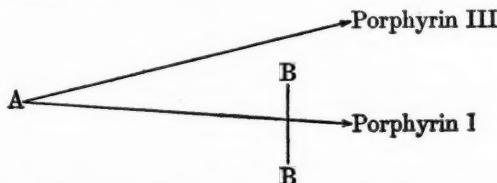
breast-feeding was allowed, a specimen of breast milk was examined. As this and a subsequent specimen of breast milk were completely free from porphyrin, breast-feeding was initiated, since it could not provide a source of porphyrins in the infant's blood or excreta. The meconium was very dark in colour, and showed considerable red fluorescence in ultraviolet light. On analysis 9.65 mg. of porphyrins were found, comprising a mixture of uroporphyrins and coproporphyrins and also tricarboxylic and dicarboxylic porphyrins (Plate 21, Fig. 1). A urinary specimen collected throughout the second day (24 ml.) contained 140 µg. of coproporphyrin, but subsequent daily specimens were porphyrin-free. The first faecal specimen collected on the third day showed red ultraviolet fluorescence, but the small quantity of porphyrin present had disappeared by the time it was possible to analyse the material.

The appearance of high concentrations of porphyrin in the infant's blood, urine, and meconium immediately after birth, with their rapid subsequent diminution, supports the conclusion that these porphyrins were derived from maternal sources *in vivo*. The normal range of values for porphyrin in the urine of the newborn, and in normal meconium, is not known, and it is therefore not possible to assess the significance of the figures obtained for them in this case. The excessive quantities of coproporphyrin and uroporphyrin I found in the blood of the child, however, constitute much more certain evidence of transplacental origin, since the normal serum-coproporphyrin at this age is 1 to 3 µg. per 100 ml. (Fikentscher, 1935), the erythrocyte-coproporphyrin is 5 to 8 µg. per 100 ml. (cord blood; Schwartz and Wikoff, 1952), and the erythrocyte-uroporphyrin I is not measurable. Three possible mechanisms could account for the increased neonatal blood-porphyrin concentration:

1. Diffusion of serum-porphyrins from the mother through the placenta.
2. Leakage of maternal red blood-corpuscles through the placenta.
3. Transplacental migration of precursor substances, and utilization of these in porphyrin synthesis by the foetus to give abnormal amounts of type I porphyrin.

The first mechanism appears the most likely one. It implies that porphyrins diffuse through the placenta throughout foetal life, not entirely freely, as there is a fall in concentration from the maternal to the foetal side, and being predominantly of type I configuration they cannot be employed in normal haemoglobin formation. Some will diffuse into the red blood-corpuscles, and will pass finally via the liver into the meconium, which in fact, in the present case, contained large quantities of uroporphyrin I and coproporphyrin I. The apparent anomaly, in both maternal and neonatal blood, of uroporphyrin being present in the corpuscles but absent from the serum, cannot at present be explained. The second mechanism might operate to a limited extent, but it is extremely unlikely that approximately one-half of the red blood-corpuscles in the newborn infant's circulation should be maternal in origin, an assumption which would be necessary if all the porphyrin in the foetal blood were due to corpuscular transplacental migration. The third hypothesis involves the passage of precursor substances through the placenta and their synthesis to copro-

porphyrin and uroporphyrin, both of isomer I configuration. Such a synthesis could take place (1) by competition for the enzyme concerned in normal synthesis of series III porphyrins, or (2) by an independent metabolic pathway employing a separate enzyme. The first mode of synthesis would be competitive in nature, and would lead to an inhibition of normal protoporphyrin-9 and haemoglobin production; no evidence of such inhibition was obtained in the present case, the haemoglobin concentration and blood picture in the infant being quite normal. The second mode of synthesis appears at variance with the generally observed parallelism in the synthesis of types I and III porphyrins, a parallelism which depends on their derivation from a common precursor. It appears possible, however, that introduction of excess of a type I intermediate (at B B in the diagram) by utilizing the normal enzymic mechanisms of the child, could result in augmented porphyrin-I production, while porphyrin-III synthesis would remain unaffected.



Our data do not allow of a decision on this point, but the similarity of the distribution of intracorporeal and extracorporeal porphyrins in maternal and infant blood at the time of birth supports the conclusion that the porphyrins themselves had migrated. It is remarkable that within six days the normal organism was able to dispose of this excess of pigments by rapid diffusion from within intact erythrocytes, and presumably by excretion mainly via the kidney; it was found impracticable to obtain urine before the second day, and the value 140 µg. was the coproporphyrin content of a 24 ml. specimen collected at that time. In contrast to the permeability of the placenta and red-cell membrane to the passage to porphyrins, the secretory alveoli of the breast appear to be completely impermeable.

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We are indebted to Dr. S. Papastamatis for his valuable help in the chromatographic procedures, and to Mr. S. Coxon and Mr. C. Howe for photographs of the chromatograms and crystalline preparations. We should also like to thank the Nursing Staff of St. Mary's Hospital, Manchester, for the care with which they collected many of the specimens examined during the course of this investigation.

Summary

1. Observations have been made on porphyrins in the blood, urine, and faeces of a female patient suffering from congenital porphyria, before and after the birth of a normal child.

2. Abnormally raised blood-porphyrin concentration was observed in the newborn infant, but on the sixth day after birth porphyrins were not measurable. The urine and faeces were normal on the third and subsequent days.
3. Porphyrin pigments were not secreted into the breast milk.
4. The evidence presented supports the conclusion that porphyrins in the maternal circulation were able to pass fairly freely through the placenta into the foetus, but that the latter was able to eliminate the pigments rapidly after birth, and suffered no ill effects therefrom.
5. Post-mortem studies showed evidence of well-marked intermediary metabolism of porphyrins in all maternal tissues, more especially in the liver and spleen, and also extensive deposits of iron-containing pigments derived from the excessive haemoglobin breakdown which had been an important feature in this case.

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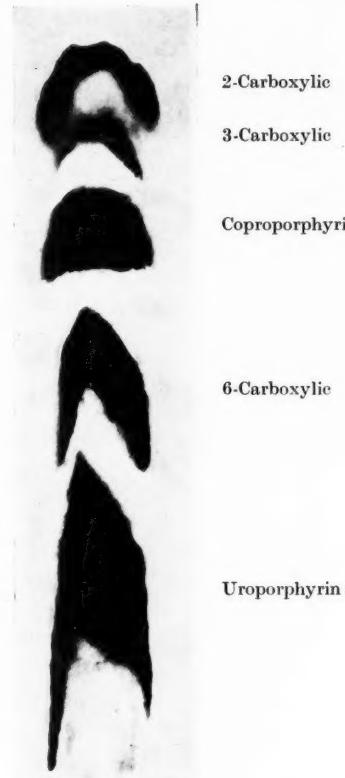
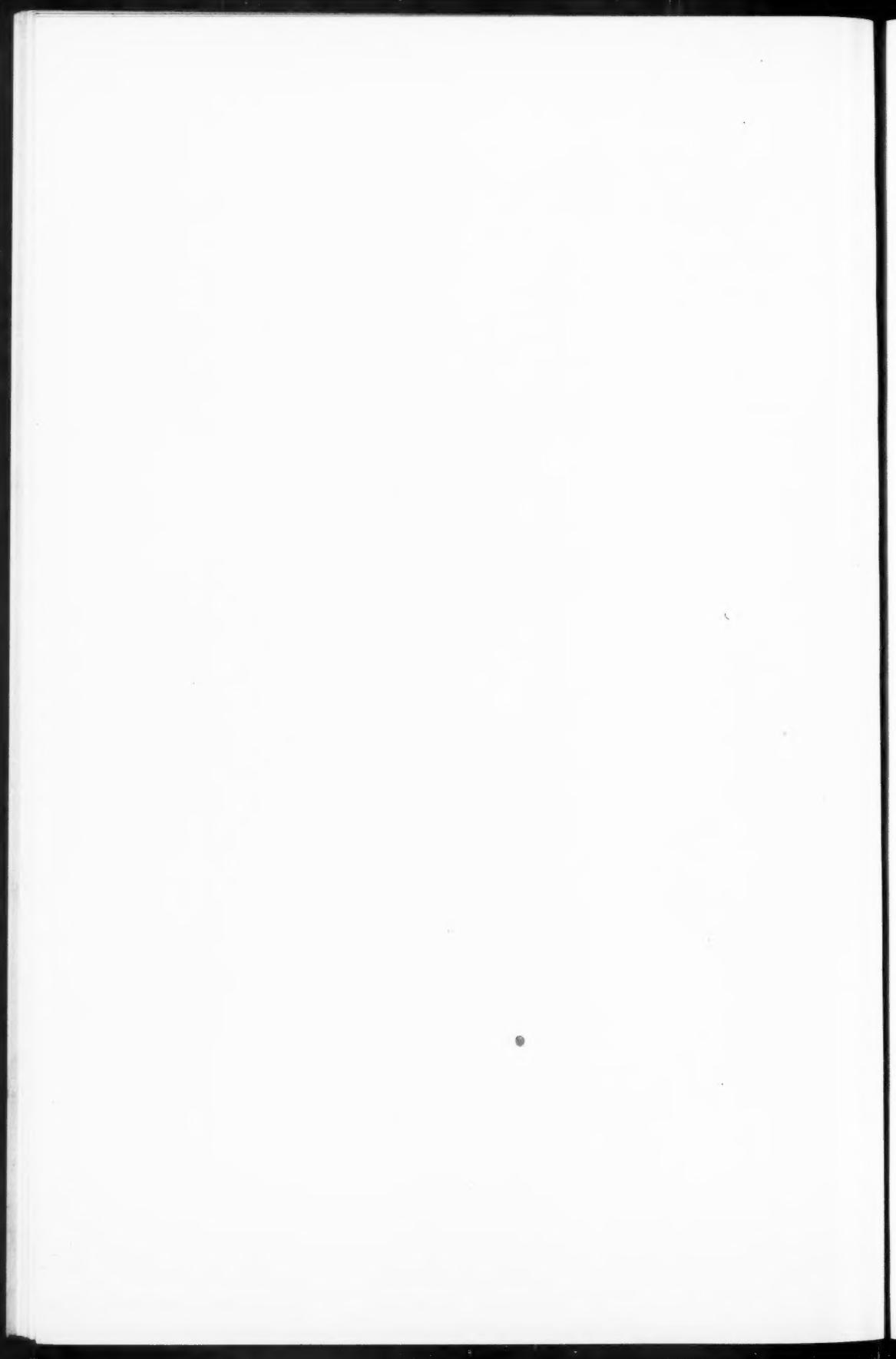


FIG. 1. Chromatographic separation of porphyrins in meconium
(method of Nicholas and Rimington, 1949)



FIG. 2. Photomicrograph of crystalline methyl ester of uroporphyrin I isolated from the liver of the patient M.S. ($\times 450$)



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BRONCHIECTASIS AND BRONCHOSTENOSIS FOLLOWING PRIMARY TUBERCULOSIS IN INFANCY AND CHILDHOOD¹

By HOWARD WILLIAMS AND CHARLOTTE ANDERSON

(From the Department of Clinical Research, The Children's Hospital, Melbourne)

With Plates 22 to 27

THE object of the present paper is to show how bronchiectasis and bronchostenosis may develop in the course of primary tuberculous infection in infancy and childhood, to outline part of the natural history of the disease, and to discuss problems of diagnosis and management. It has been established that the hilar and mediastinal lymph-glands of the primary pulmonary tuberculous complex may involve the adjacent bronchial wall by compression, by infiltration, or by actual perforation with discharge of the caseous content of the gland into the bronchial lumen. Rössle (1936), Terplan and Hyde (1940), and Rich (1944) have demonstrated these features in post-mortem material, and Morlock and Pinchin (1933), Jones, Rafferty, and Willis (1942), Görgényi-Göttche and Kassay (1947), Hutchison (1949), and Veeneklaas (1952) have shown by bronchoscopic examination different phases of involvement of the bronchus. Hutchison (1949) classified the changes seen bronoscopically in three main types: first, local bulging of part of the wall due to pressure from an enlarged gland; second, development of tubercles or a tuberculoma under the mucous membrane of the bulging bronchial wall, owing to invasion of the bronchus; third, perforation of the bronchus by the gland, the sinus later becoming surrounded by granulation tissue of variable amount and appearance. These stages may be seen at different times in one patient. Bronchial involvement commonly, but not invariably, causes obstruction in the bronchus from bulging of the wall, from a tuberculoma, from granulation tissue round a perforating sinus, or from caseous material aspirated from the gland. If the bronchial lumen is narrowed sufficiently, emphysema of the distal lung occurs, as air cannot be adequately expelled past the obstruction, but if the lumen is completely obliterated resorption collapse develops. Barsby (1941), Meneghelli and Smith (1943), Richards (1944), Görgényi-Göttche and Kassay (1947), Graham and Hutchison (1947), and Veeneklaas (1952) have all described aspects of these occurrences as studied by bronchoscopic and radiological examination. Perforation of the bronchus by the gland results in discharge of the caseous content into the lumen, and aspiration of this material into the distal lung causes inflammation of very varied pattern. The inflammation may be mild and completely resolve, or may

¹ Received October 21, 1952.

suppurate and cause caseation, and so result in cavitation, fibrosis, and calcification. Resorption collapse due to bronchial obstruction, and consolidation due to the inflammatory reaction from the inhalation of caseous glandular contents, can both produce the clinical and radiological pattern of the 'epituberculosis' of Eliasberg and Neuland (1920). The evidence seems to favour resorption collapse as the commoner cause of the large segmental or lobar opacities seen in radiographs of the lungs of infants and children with primary tuberculous infection.

With healing of the tuberculous glands restoration of the normal lumen of the bronchus usually occurs, but structural damage in some patients may be of such a degree that replacement by fibrous tissue results in a permanent stenosis. Lightwood and Wilson (1936) described a patient who had stenosis of the left bronchus with bronchiectasis, fibrosis, and calcification in the left lung. Richards (1944), Graham and Hutchison (1947), Brock (1950), and Veeneklaas (1952) have all described bronchial stenosis following tuberculous infection. As resolution of the lesion causing bronchial obstruction is slow, permanent lung collapse is common and is usually accompanied by bronchial dilatation. Resolution of tuberculous pneumonitis, with or without an obstructing bronchial lesion, is similarly slow, and again permanent collapse, fibrosis, and bronchiectasis commonly develop. Kent (1942), Jones, Peck, and Willis (1946), Graham and Hutchison (1947), Brock (1950), Roberts and Blair (1950), and Veeneklaas (1952) have all demonstrated bronchiectasis following collapse or consolidation of lung due to bronchial lesions in tuberculous infection. If inflammation has occurred in the lung from aspiration of caseous glandular material, either complete resolution, or caseation, cavitation, and fibrosis may occur, according to the nature and severity of the reaction. The clinical and pathological observations here recorded show how bronchial involvement by tuberculous glands causes either absorption collapse or aspiration pneumonitis, or both, and how residual changes commonly occur in the form of bronchiectasis and bronchostenosis.

Patients and Methods of Investigation

During a five-year period (1947-51) a study was made of 40 patients with primary pulmonary tuberculosis in whom either pulmonary collapse or consolidation occurred. One other patient with long-standing post-tuberculous bronchiectasis and bronchostenosis was also studied. All the patients were between the ages of five months and 12 years; seven were under one year, 21 between one and three years, seven between three and six years, and 15 between six and 12 years of age. The method of study was to follow the natural history of the disease by clinical observation and serial radiographic, bronchoscopic, and bacteriological examinations. Radiological examinations included antero-posterior and right and left lateral films in all patients and, when necessary, oblique views. Short exposures of one-fiftieth of a second, made by a rotating anode tube, eliminated movement and gave films of good quality and definition. Bronchoscopic examinations under general anaesthesia were carried out in the X-ray theatre with standard Jackson bronchoscopes. Anaesthesia was induced

by giving either bromethol rectally (0·1 ml. 'avertin' per kg. of body-weight) or thiopentone intravenously, and was maintained by an ether and oxygen mixture. After bronchoscopic examination a catheter was placed in the main bronchus on the affected side, iodized oil was introduced under screen control, and suitable films were taken. This procedure has proved to be both safe and satisfactory, and free from complications. Bacteriological culture of the fasting gastric contents, and in some patients of the bronchial mucus, for *M. tuberculosis* was conducted by a modified Petragnani technique (Webster, 1941). A Mantoux test with 0·1 ml. of 1:1000 old tuberculin was carried out in all patients.

Pathology

Thirty-five of the 40 patients with pulmonary collapse or consolidation were examined bronchoscopically and radiologically at an early stage of the disease;

Analysis of 40 Patients who had Primary Tuberculous Infection with Segmental or Lobar Radio-opaque Pulmonary Shadows

<i>Radiological lesion: lobe affected</i>	<i>Bronchial lesion</i>	<i>Sequelae (32 cases)</i>
1. Collapse		<i>Bronchiectasis: lobe affected</i>
R. upper 10	1. Bulging of the wall 12	R. upper 9
R. middle 2	2. Tubercles or tuberculoma 10	R. lower 3
R. lower 4	3. Granulation tissue 9	R. middle 2
L. upper 8	4. Block shown by broncho- graphy alone 1	L. upper 6
L. lower 3	5. No bronchial lesion demon- strated 8	L. lower 3
R. upper and R. middle . . . 4		R. upper and R. middle . . . 3
R. upper and R. lower . . . 1		R. upper and R. lower . . . 1
R. middle and R. lower . . . 4		R. middle and R. lower . . . 4
L. upper and L. lower . . . 1		L. upper and L. lower . . . 1
2. Consolidation		<i>Bronchostenosis: bronchus affected</i>
L. upper 2½		Right 5
R. upper 1½		Right and middle-lobe . . . 1
Total 40	Total 40	Right dorsal-lobe . . . 1
		Left 2
		Lingular 1

the remainder were not bronchoscopically examined until later, either when the pulmonary lesion had been present for over a year, or when it showed radiological evidence of resolution. Thirty-two of the 35 patients who were examined at an early stage of the disease had a bronchial lesion which reasonably accounted for the pulmonary changes; the remaining eight patients had no such lesion. Thirty-two of the 40 patients developed permanent bronchiectasis, and 10 permanent bronchostenosis. Twenty-eight of the 40 patients yielded positive cultures of *M. tuberculosis*. In 21 the culture was obtained from the fasting gastric contents, and in seven from aspirated bronchial mucus. Gastric culture was undertaken in all patients, and bronchial aspiration in 13. Bronchial mucus gave a positive culture in seven patients in whom the gastric contents yielded no growth. The Mantoux test was positive in all patients. The Table shows the various lobes involved, the bronchial lesions demonstrated, and the sequelae.

The relationship of segmental or lobar opacities to bronchial lesions. Of the group of 35 patients who were studied in the early phase of the disease, 32 showed radiological evidence of pulmonary collapse and three of consolidation.

Nine of these patients had emphysema of a lobe or segment before collapse developed. Thirty-one of this group of 35 patients had an obstructing lesion of the bronchus, seen both on bronchoscopic and bronchographic examination, which accounted for the radiological and clinical findings; in one other an obstruction of a segmental bronchus was seen bronchographically, while three had no demonstrable lesion. The bronchial lesions seen on bronchoscopic examination were of three main types. First, 12 patients showed local bulging of one or both sides of the bronchial wall, the lumen being either reduced to a slit or completely occluded. The mucosa in the bulging area was sometimes normal in appearance, but more often red, congested, and oedematous, and covered with mucopurulent exudate. Second, in 10 patients the bronchial mucosa was red and swollen, with several submucosal yellowish areas the size of a pin's head, or else a reddish granulating mass with yellow points protruded into the lumen. In eight patients this granulating mass, or the tubercles, could be partially removed by aspiration. The aspirated material consisted of granulation tissue, with flecks of caseous material which was sometimes partially calcified. *M. tuberculosis* was seen in a smear of this material in three patients. Third, in nine patients pale, watery-looking granulations partially or completely occluded the bronchial lumen. This granulation tissue was usually non-specific chronic inflammatory tissue. In three of these patients caseous material could be aspirated by a catheter which passed through a bronchial sinus into the caseous gland. In two other patients thick tuberculous pus was aspirated distally from the bronchus, which was almost completely occluded by granulation tissue.

The bronchus most commonly involved was the right, but the orifices of each of the lobar divisions of the right and left bronchi were observed to be affected in different patients. Correlation of the bronchoscopic lesions with the segment or lobe of the lung involved showed that in 32 of the 35 patients the lung lesion seen radiographically was primarily due to bronchial obstruction, from bulging of the wall, from a tuberculoma, or from granulation tissue. In those patients in whom a caseous gland had ruptured into the bronchus it is very probable that there was an inflammation in the collapsed lobe from aspiration of caseous material and tubercle bacilli. In the remaining three patients no definite bronchial lesion other than reddening and swelling of the bronchial orifice was observed, while a bronchogram demonstrated a collapsed bronchiectatic segment. The five patients who were not examined bronchoscopically until a later stage of the disease also showed no evidence of bronchial obstruction. The only abnormality was reddening and a little oedema of the bronchial orifice leading to the lobe involved. In each case iodized oil passed freely into the lobe, and demonstrated bronchial dilatation. It is probable that examination at an earlier stage of the disease would have demonstrated a bronchial lesion.

Bronchiectasis. Permanent collapse and bronchiectasis followed in 32 of the 40 patients who had pulmonary collapse or consolidation. In the remaining eight patients, in whom the collapsed lobe re-expanded, the pulmonary shadow was present for less than six months. In some patients proof of the bronchiectasis following collapse or consolidation was only obtained by a bronchogram,

because plain chest röntgenograms often gave little or no evidence of the presence of the lesion. Frequently a retracted, uninjected bronchiectatic segment did not throw a shadow of sufficient contrast to be identified by routine chest röntgenograms. While, in the majority of the patients, bronchiectasis appeared to develop from collapse due to focal bronchial obstruction, in some patients tuberculous infection of the lung also occurred. In two patients with lobar collapse thick pus, from which *M. tuberculosis* was readily cultivated, was found behind granulation tissue. The final state of healing in these two patients was a stricture of the right and left bronchus respectively, and the distal lobes were shrunken and bronchiectatic, with areas of scattered calcification (Plate 22, Figs. 1, 2, and 3). In other patients, in whom the bronchial obstruction had resolved spontaneously or had been cleared by bronchoscopic suction, the lung parenchyma distal to the lesion still remained radio-opaque, and resolution was slow. In a few of these patients a growth of *M. tuberculosis* could still be obtained from the bronchial mucus after the bronchial lesion was soundly healed. It must be concluded that these patients had a low-grade tuberculous pneumonitis in a collapsed lobe. The distribution of the post-tuberculous bronchiectatic lesions (see Table) was widespread, and every lobe or segment was involved. Although the bronchiectasis has been described in the Table as affecting a lobe, often only one segment of that lobe was involved; frequently, for example, only the anterior segment of the right upper lobe, or only the lingula, or the anterior and lingular segments of the left upper lobe, were involved. The right lung was affected more than twice as often as the left, and the upper lobes of both lungs more often than the lower. In nine patients segments of two different lobes were involved. The involvement of segments of different lobes was difficult to explain; for example, how did bronchiectasis come to affect the dorsal segment of the right lower lobe and the anterior segment of the right upper lobe, or how were the anterior segment of the right upper lobe and the middle lobe involved? We have not observed involvement of different segmental bronchi by separate tuberculous lesions. But extensive involvement of either main bronchus, especially the right, can result in obstruction both of the upper-lobe and of the middle-lobe bronchus, or of the upper-lobe and the dorsal-lobe bronchus, thus accounting for two different segmental lesions (Plates 23 and 24, Figs. 4, 5, 6, and 7). In addition a perforating lesion of either bronchus, with discharge of caseous debris into the lumen, has resulted in plugging of separate segmental bronchi, leading to absorption collapse. Only two uninjected bronchiectatic lobes have been examined histologically, as in other cases there has been no definite indication for their surgical removal. The lobes in both cases showed moderate dilatation of both bronchi and bronchioles, but the mucosa, submucosa, muscle, elastic tissue, and cartilage were histologically normal. The alveoli were collapsed; there was increased fibrous tissue, with aggregations of small round cells, in the adventitia of some of the smaller bronchioles, and also between some of the collapsed lobules.

Bronchial stricture. In 22 of the 32 patients who had a demonstrable bronchial lesion complete resolution occurred, leaving a normal bronchial lumen, so that it

was impossible to detect the site of the previous lesion on bronchoscopic examination. In the remaining 10 patients the tuberculous process caused sufficient damage to leave a permanent narrowing or stricture of the bronchus. In five patients the right bronchus was involved, in two the left bronchus, in one the right and middle-lobe bronchi, in one the right dorsal-lobe bronchus, and in one the lingular bronchus. All these strictures have been demonstrated both bronchoscopically and by bronchogram. One of these patients had a primary tuberculous infection at the age of four months, and the right bronchus became narrowed from infiltration by the hilar glands. A stricture of the right bronchus developed just above the upper-lobe orifice, together with permanent collapse of the right middle lobe. Three years after the original infection right pneumonectomy was undertaken, as it was considered that the stricture was a potential danger. Unfortunately the patient died 12 hours after the operation. The specimen (Plate 27, Figs. 12 and 13) showed a narrowed right bronchus at the level of, and immediately above, the upper-lobe orifice, and a collapsed bronchiectatic middle lobe. The narrowing was due to fibrous tissue in the bronchial wall, and enclosed in this fibrous tissue was calcified caseous material.

Clinical Features

There may be no symptoms at any stage during the development of bronchiectasis or bronchostenosis from the primary tuberculous complex. It is well known that patients with the primary complex may at no stage develop either constitutional or pulmonary symptoms. Four of our patients who had involvement of a bronchus by the tuberculous glands, and who subsequently developed bronchiectasis, were free from symptoms during the entire period of the disease. These patients were investigated as 'contacts' of an adult who had a pulmonary infection, or were found to have a positive Mantoux test during a Mantoux survey at school. The only means of knowing that the primary infection was progressing and causing a bronchial lesion, with subsequent bronchiectasis, was by serial radiological and bronchoscopic examination. The following case history illustrates the development of 'silent' collapse, due to bronchial compression, and subsequent healing leaving a bronchiectatic lobe.

Case 1. R. R. was examined at the age of 17 months in March 1948 because his mother was found to have pulmonary tuberculosis. The infant had always been healthy, and had developed normally. A general clinical examination and an X-ray examination of his chest gave normal results, but the Mantoux reaction with 1:1000 old tuberculin was strongly positive. Culture of the fasting gastric contents for *M. tuberculosis* gave a negative result. In May 1948 radiological examination of the chest showed an enlarged left hilar shadow, and an X-ray in September 1948 demonstrated collapse of the left lower lobe. Bronchoscopic examination showed the left bronchus below the dorsal-lobe opening to be occluded, the lumen being reduced to a mere slit; the mucosa was oedematous and congested, but no tubercles were seen. Culture of bronchial washings resulted in a growth of *M. tuberculosis*. During this time the child was perfectly well, had no cough, and gained weight. During the next 10 months until June

1949 he remained well; the left lower lobe remained collapsed, but gradually partial clearing of the dense radio-opaque shadow occurred. Bronchoscopic examination in July 1949 showed a patent left bronchus with normal mucosa, but a bronchogram showed crowding and cylindrical dilatation of the bronchi of the three basal segments of the left lower lobe. From July 1949 to December 1951 he has been well, and has grown and gained weight steadily. During the latter period he contracted the common respiratory-tract infections of childhood, including pertussis, but they all cleared promptly, and there has been no tendency for secondary infection to occur in the bronchiectatic lobe. Bronchoscopic examination and a bronchogram in April 1951 showed findings identical with those of the examination in July 1949.

There seems to be little doubt that, if this boy had not been investigated as a 'contact' for tuberculous infection, his bronchiectasis would not have been discovered. Furthermore, if the course of the disease had been followed only by serial X-rays, the collapsed lobe would have been considered to have resolved; for the only evidence of a residual lesion was a little crowding and streakiness of the broncho-vascular bundles in the region of the left lower lobe as seen in the left lateral röntgenogram of the chest.

Symptoms consequent on bronchial involvement by tuberculous glands. The majority of patients with a lesion of the bronchus had a cough, and many also had a wheeze. It is strange that the cough-reflex is not excited in every patient. The cough was commonly dry and irritating, and usually persisted for months or even for a year or more. It disappeared usually as the bronchial lesion resolved, but in some patients before resolution was complete. Wheezing occurred frequently, and was due to narrowing of one of the main bronchi. It was often loud, and usually the expiratory phase was as loud and prolonged as the inspiratory sound. Increased respiratory effort due to laughing, crying, excitement, exercise, or sucking caused the wheeze to become louder. In some patients the wheeze was intermittent, for during periods of rest or sleep it could not be heard, but when respiration was increased it became audible. This intermittent character sometimes led to a mistaken diagnosis of asthma. An infant with a chronic, dry, irritating cough accompanied by a wheeze should always be suspected of having a narrowed or partially occluded bronchus, and a common cause is tuberculous infection. The physical signs accompanying bronchial involvement depend on the stage and degree of bronchial occlusion. Emphysema, collapse, or consolidation may occur in one or more segments or lobes, singly or in sequence, so that the clinical and radiological patterns may be bewildering. One week a lobe may be emphysematous, the next collapsed, and the following week it may re-expand. Emphysema, collapse, or consolidation was detected clinically only if the lesion was sufficiently large. Segmental lesions were rarely detected clinically, being too small to produce alteration in the percussion note and breath sounds. Lobar lesions were usually of sufficient size to be detected clinically, but the signs were often slight. In emphysema the percussion note was more resonant, and the breath sounds diminished; in collapse or consolidation the percussion note was impaired, and the breath sounds usually diminished, but sometimes bronchial in character. Frequently the mediastinum was not displaced towards the side

of the collapsed lobe, and displacement if present was difficult to detect clinically. The absence of mediastinal displacement in some patients was probably due to a slow development of collapse, compensatory emphysema of the adjacent lung filling the reduced thoracic space. Most of the clinical signs were slight compared with the gross signs in the röntgenogram of the chest.

The following case history illustrates infiltration and obstruction of the right bronchus by caseous hilar glands, causing first obstructive emphysema of the right lung and then collapse of the right lower and middle lobes. Subsequently the glands perforated the right bronchus, which became occluded by granulation tissue, and tuberculous suppuration occurred in the collapsed lobe. Eventually healing resulted in a gross narrowing of the right bronchus and shrinking, fibrosis, calcification, and bronchiectasis of the right lower and middle lobes.

Case 2. D. D., a healthy male baby, had a cough and wheeze in June 1948, when he was aged 15 months. These symptoms were attributed by his family doctor to an inhaled foreign body, as the infant had frequently been observed to put small toys and other objects in his mouth. He was not constitutionally ill, and loud rhonchi were heard in inspiration and expiration over both sides of his chest. Radiological examination showed obstructive emphysema of the right lung, and his Mantoux reaction with 1:1000 old tuberculin was strongly positive. Bronchoscopic examination showed a blunt carina major and a red, swollen right main bronchus, the lumen of which was seen as a mere slit during the inspiratory phase of respiration, but on expiration was completely obliterated. During the next two months the right upper lobe collapsed, and subsequently the right middle lobe. The right upper lobe then re-expanded, and the right lower lobe, which was previously emphysematous, collapsed. During this time the child did not seem sick, but had a slight pyrexia, and his weight remained unchanged. He was given a course of streptomycin (20 mg. per kg. of body-weight daily) for 10 weeks, but there was no change in his clinical condition or in the physical signs in his chest. During the next year he slowly gained weight, and seemed fairly well; the wheeze disappeared, but he still had a little spasmodic cough. The right lower and middle lobes remained collapsed, and gradually further retraction occurred. The heart and mediastinum shifted to the right, and the right side of the diaphragm became more elevated. In August 1949 bronchoscopic examination showed a blunt, short carina major, and the right bronchus immediately below the level of the upper-lobe orifice was almost completely obstructed by watery-looking granulation tissue. A very small central opening allowed a fine catheter to be introduced, and 10 ml. of thick pus were aspirated; the pus on culture yielded a profuse growth of *M. tuberculosis*. This was surprising, for the boy was clinically well. From August 1949 to November 1950 he steadily gained weight, his cough disappeared, and he was very well. During this time air entry on the right side of the chest was much improved, the right lower and middle lobes retracted further, and calcification developed in these lobes and in the right paratracheal glands. Bronchoscopic examination showed an advanced degree of stenosis of the right bronchus immediately below the level of the upper-lobe orifice, and a bronchogram showed an emphysematous right upper lobe and grossly retracted bronchiectatic lower and middle lobes, with a severe degree of stenosis of the right bronchus. During the next year to November 1951, when he was four and three-quarters years old, he was very well and active. He had contracted several colds, and also measles, but had recovered promptly from these infections. Bronchoscopic

and bronchographic examination showed a state of affairs identical with that in November, 1950 (Plate 22, Figs. 1, 2, and 3).

Constitutional symptoms. Most of the children had constitutional symptoms during the period of bronchial involvement. Lack of energy, tiredness, poor appetite, failure to gain weight, irritability, and low-grade pyrexia were the common features. Some parents merely stated that the child did not seem quite so well as usual. In the majority of the patients these symptoms were associated with a cough, and some also had a wheeze.

Symptoms and signs due to bronchiectasis and bronchostenosis when the primary tuberculous complex has healed. When the primary tuberculous complex had healed, almost all of the patients were free of symptoms, were healthy, and developed normally. The absence of symptoms was attributed to lack of pyogenic or tuberculous infection in the collapsed, retracted, and bronchiectatic segment or lobe. Usually no abnormal physical signs were detected clinically, but if present they were slight, and consisted of either a few crepitations or slight alteration of the breath sounds over the affected segment or lobe. Radiologically the segment or lobe involved showed crowding and 'hardening' of the lung-markings, and these markings extended from the hilum to the periphery of the lung field. Lateral röntgenograms were necessary for the detection of some of the lesions, because the retracted bronchiectatic lobe or segment was frequently hidden behind the heart shadow in anteroposterior films. With experience it was possible to suspect bronchiectasis in some patients, in whom small irregular 'cystic' spaces could be seen in the crowded, accentuated lung-markings; but unless a bronchogram was done it was not possible to be sure of the diagnosis in many patients. The following case history, with X-rays and bronchograms, illustrates a tuberculous lesion of the right bronchus, with collapse of the right middle lobe and pneumonitis in the upper lobe, and its healing which left only slight scarring and calcification in the right upper lobe. The child remained free of respiratory symptoms for six and a half years, after which further investigation disclosed stenosis of the right bronchus, and bronchiectasis of the anterior segment of the right upper lobe and medial segment of the middle lobe.

Case 3. In October 1943 D. T., aged 20 months, was examined for tuberculous infection because her father had developed pulmonary tuberculosis. She had not been well for several months, but had no cough. Her Mantoux reaction with 1:1000 old tuberculin was positive, and X-ray examination of her chest showed enlargement of the right hilar shadow, collapse of the right middle lobe, mottling in the right upper lobe, emphysema of the right lower lobe, and shift of the heart and mediastinum to the right (Plate 23, Fig. 4). Bronchoscopy examination showed that the right bronchus was narrowed to a slit from bulging of the anterior and lateral parts of the wall. The upper-lobe orifice was partially occluded by this swelling, and the middle- and dorsal-lobe orifices could not be seen. From October 1943 to May 1944 she remained well, and the X-ray appearances in the chest remained unchanged. Gradually partial clearing of the lesion in the chest occurred, leaving some streakiness, calcification, and a slight 'honeycomb' appearance in the region of the anterior segment of the right upper lobe, some calcification in the right paratracheal glands, and slight displacement

of the heart to the right. In January 1945, at the age of three years, she lost her appetite, failed to gain weight, and began to pass loose, bulky, greasy stools, and the abdomen became distended. These signs and symptoms were attributed to malabsorption, due possibly to tuberculous lymphadenitis of the mesenteric glands. The cause was finally shown in September 1950 to be a tuberculous enteritis. During the period from her initial tuberculous infection to the age of eight and a half years there were no symptoms referable to the respiratory tract. The tuberculous enteritis responded satisfactorily to streptomycin (40 mg. per kg. of body-weight) and *p*-aminosalicylic acid (4 gm. daily) given for a period of six months. Investigation of the chest lesion at the age of eight and a half years showed a stricture of the right bronchus, and bronchiectasis of the anterior segment of the right upper lobe and medial segment of the middle lobe (Plates 23 and 24, Figs. 5, 6, and 7). It is almost certain that the tuberculous glands which invaded the right bronchus also caused collapse of part of the middle and upper lobes from involvement of the corresponding bronchi.

One other patient had an exactly similar lesion, and another a stricture of the right bronchus with complete collapse of the right middle lobe. In the latter patient a large calcified gland was in juxtaposition to the bronchial stricture, and obliterated the middle lobe bronchus (Plate 25, Figs. 8 and 9). Chronic pyogenic infection in the bronchiectatic lung, or in the lung distal to a broncho-stenosis, has not occurred in our patients, although all have contracted the common respiratory-tract infections of childhood, and some have had pertussis and measles. Only three of the 32 patients developed infection in the affected lung, and in them it resolved after a period of two to four weeks.

One patient came to us suffering from a chronic tuberculous lung infection with pulmonary cavitation, bronchiectasis, and stenosis of the right bronchus.

Case 4. R. S., a boy aged five years, who had never had any severe illness and had always been active and healthy, had a mild respiratory-tract infection in October 1948, and his family doctor was surprised to find many adventitious sounds and bronchial breathing over his right lung. A röntgenogram of his chest disclosed a grossly collapsed right lung with cavities, and the mediastinum displaced well to the right (Plate 26, Fig. 10). The Mantoux reaction with 1:1000 old tuberculin was strongly positive, and culture of the fasting gastric contents yielded *M. tuberculosis*. His temperature was normal, he was well-developed and well-nourished, and he was not constitutionally ill. It seemed strange that a lesion apparently so gross could exist with no symptoms and with no antecedent history. Bronchoscopic examination showed a stenosis of the right bronchus below the middle-lobe bronchus, and a bronchogram showed collapse, with gross cavitation and bronchiectasis, of the right lower lobe, and collapse and bronchiectasis of the two remaining right lobes. Observation for a period of six months showed that the boy was not constitutionally ill, but intermittently he had a low-grade pyrexia. As gastric culture for *M. tuberculosis* was persistently positive, and the right lung had large cavities, pneumonectomy was carried out in April 1949 after a course of six weeks' streptomycin therapy (20 mg. per kg. of body-weight per day). Convalescence was uneventful, and the boy was well and active when last seen in November 1951. Gastric culture for *M. tuberculosis* was negative, and a röntgenogram and clinical examination of the left lung were normal. Examination of the right lung showed a small, collapsed lung, with stenosis of the right main bronchus and extensive bronchiectasis, cavitation, fibrosis, and caseation (Plate 26, Fig. 11).

It is probable that this child had a 'silent' primary tuberculous infection, with ulceration of a gland into the right bronchus. Low-grade tuberculous pneumonitis slowly destroyed the right lung, and left a shrunken, fibrotic, bronchiectatic lung, with a stricture of the right bronchus. The source of tuberculous infection was not discovered.

Treatment

In the early stages of the disease the patients were rested in bed. Some children were treated at home, because they could be adequately cared for and did not require special treatment, and no infected adults were in the home. It was necessary to treat the larger number in a convalescent hospital which had adequate educational and occupational facilities. Rest for a period of six to 12 months was considered advisable, since healing of the tuberculous process, as judged by bronchoscopic examination, was slow. General well-being, satisfactory gain of weight, and freedom from symptoms proved to be the most reliable indications of favourable progress, and more important than blood-sedimentation rates or minor changes in the röntgenograms of the chest. The persistence of radio-opaque segmental or lobar lesions may be no sufficient reason for continuing rest; for the bronchial lesion frequently healed long before the lung lesion cleared. Bronchoscopic aspiration of granulation tissue, tuberculoma, or caseous material from the gland was carried out in 19 patients. This procedure was safe, and did not disturb the patient. Its efficacy seemed limited, for re-aeration of a collapsed lobe occurred in only four patients after the bronchial lumen had been restored. Failure of re-expansion was probably due either to an associated inflammatory reaction in the collapsed lung, or to the length of time for which collapse had existed. In the 12 patients in whom the bronchus was narrowed by bulging of the wall, restoration of the lumen was not possible. There is no way of distinguishing by clinical and radiological evidence the patients who are likely to receive benefit from bronchoscopic aspiration. Streptomycin therapy was used in 15 of the 40 patients. In six patients the dose was 40 mg. per kg. of body-weight daily, and was continued for four to six months; in nine it was 20 mg. per kg. of body-weight for a period of five to 14 weeks. Experience with this small group of patients has suggested that streptomycin is of doubtful value. Four patients who had tuberculous granulation tissue in the bronchus, and who received large doses of streptomycin for a period of over four months, did not show a more rapid rate of healing than would have been expected from natural means. Two other patients developed collapse of a lobe, with ulceration of a tuberculous gland into the bronchus, while receiving streptomycin therapy for miliary tuberculosis. On theoretical grounds it seems unlikely that healing in the caseous gland can be promoted by streptomycin, as there is no blood-supply to the caseous tissue, and the solubility of streptomycin in lipoid material is very low. The efficacy of streptomycin in aiding healing is doubtful, and an opinion cannot be given on the basis of the present findings. Until more evidence is available, it seems wiser to give streptomycin when there is ulceration of a gland into the bronchus or infiltration of the bronchial wall.

Treatment of patients who have bronchiectasis and bronchostenosis. Children with a collapsed bronchiectatic lobe or segment have been almost invariably symptomless, and secondary infection has rarely occurred; we have therefore not advised surgical treatment. Special general or medical care has not been necessary, as the children rapidly recover from the numerous respiratory-tract infections of childhood, and those who have had measles or pertussis have not fared differently from normal children. In only three of our 32 patients has secondary infection occurred in the bronchiectatic lung, and in all three cases recovery in a few weeks followed treatment with penicillin. The problem is more difficult if there is stenosis of the bronchus. If stenosis has reduced the lumen to a very small size, it seems likely that chronic secondary infection will occur sooner or later. So far, secondary pyogenic infection has not occurred in our patients who have stenosis of the bronchus. It seems wiser to defer surgical treatment until the child is old enough to co-operate adequately with the physiotherapist, and until respiratory-tract infections are less frequent. If the stenosis is mild, observation is all that is required.

Discussion

The percentage of patients who develop bronchiectasis and bronchostenosis, after involvement of a bronchus by tuberculous glands and collapse or consolidation, or both, of the affected lobe or segment, is strikingly high. Most writers (Jones, Peck, and Willis, 1946; Roberts and Blair, 1950; Veeneklaas, 1952) agree with this opinion, but Meneghelli and Smith (1943) and Macpherson and Lutwyche (1950) reported complete resolution of the majority of collapsed lobes after tuberculous infection. It is very likely that, if the patients of the latter authors had been investigated bronchographically, sequelae would have been found. Routine radiological examination is of limited value as a method of assessing complete resolution of an area of collapse or consolidation, for in some patients a collapsed bronchiectatic lobe or segment can only be found by bronchography (Case 3, Plates 23 and 24, Figs. 4 to 7; Plate 27, Fig. 14). About twice as many bronchiectatic segments or lobes were on the right side as on the left in the present series of patients, and the upper lobes of both lungs were more frequently involved than the lower. The wide scatter of lesions was similar to that described by Jones, Peck, and Willis (1946), Roberts and Blair (1950), Görgényi-Göttche and Kassay (1947), and Veeneklaas (1952). Brock (1950) and Richards (1944) showed in a considerable number of patients that the middle lobe was most commonly involved. Brock described 60 cases out of 93 in which the middle lobe was affected, and attributed this high incidence of middle-lobe lesions to anatomical peculiarities of the middle-lobe bronchus. His patients were chiefly adults, who had acquired their primary infection many years previously, and it is possible that his material did not represent a true cross-section of segmental or lobar lesions as seen in children. Brock also assumed that calcified glands in the hilar region and a bronchiectatic middle lobe were always associated, and were due to one common cause, tuberculosis. This may not be

so, for middle-lobe bronchiectasis is not uncommonly due to causes other than tuberculosis, and the incidence of tuberculous infection in adults in the British Isles is very high. In the absence of bacteriological proof the matter cannot be decided with certainty. Most workers (Jones, Peck, and Willis, 1946; Richards, 1944; Graham and Hutchison, 1947; Roberts and Blair, 1950; Veeneklaas, 1952; and the present authors) agree that secondary pyogenic infection in the collapsed bronchiectatic lobes is uncommon, but no writer has followed up a group of such children for many years. The cause of this apparent freedom from secondary infection is certainly not lack of opportunity, for respiratory-tract infections due to virus and bacterial infection are common in young children, and pertussis and measles occur frequently. Lesions involving the segments which drain against gravity seem to be as free from infection as those in the upper lobes. The freedom of bronchiectatic segments or lobes from infection is not understood, but may be due to lack of destruction of the essential bronchial and bronchiolar structure. In our two patients in whom the affected segment was examined histologically it was remarkable that the mucosa, submucosa, elastic tissue, muscle, and cartilage were normal. Tuberculous bronchiectasis does not seem to play a significant role in the aetiology of suppurating bronchiectasis. The latter disease is common in children in Melbourne, yet it is only occasionally that one finds a positive Mantoux test in such a child; of over 300 cases five were positive. A recent extensive Mantoux-test survey of Melbourne school-children under the age of 12 years showed that about six per cent. of the children gave positive reactions.

Summary

1. Caseous hilar glands of the primary tuberculous complex not infrequently compress, infiltrate, or perforate an adjacent bronchus.
2. Bronchial occlusion with pulmonary collapse may follow either compression, inflammatory swelling of the wall, granulation tissue in the lumen, or plugging from aspirated caseous material.
3. Pneumonitis may occur from aspiration of caseous glandular material, tubercle bacilli, or granulation tissue.
4. Pulmonary collapse is usually of long duration because resolution of the caseous glands, and of tuberculous infiltration of the bronchus, is slow, with the result that permanent collapse with bronchiectasis is common.
5. Pneumonitis from aspiration of the contents of the tuberculous gland may result in bronchiectasis, calcification, and fibrosis, or in suppuration and cavitation.
6. Bronchostenosis may result from healing of tuberculous infiltration of the bronchial wall.
7. Any segment or lobe and any bronchus may be involved in these changes; bronchiectasis occurs in the right lung twice as frequently as in the left, and in the upper lobes more often than in the lower; bronchostenosis most commonly involves the right bronchus.

8. The bronchiectasis is dry and symptomless, and rarely becomes chronically infected so as to produce the suppurating bronchiectasis which is common in childhood.
9. Bronchostenosis and bronchiectasis probably do not require surgical resection unless chronic secondary infection develops.

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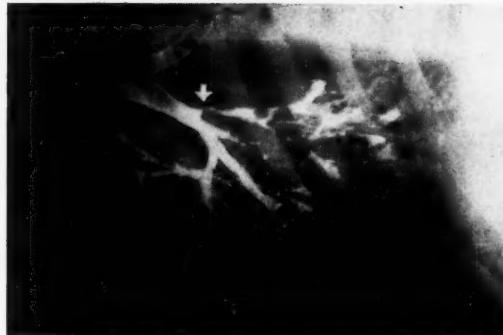


FIG. 3. Case 2, D.D., aged 4½ years (November 1951); the patient was well and had no symptoms. Bronchogram showing stenosis of the right bronchus, with collapsed, bronchiectatic, partially calcified, right lower and middle lobes and emphysematous upper lobe. Bronchoscopy examination showed gross stenosis of the right bronchus, otherwise no abnormality.

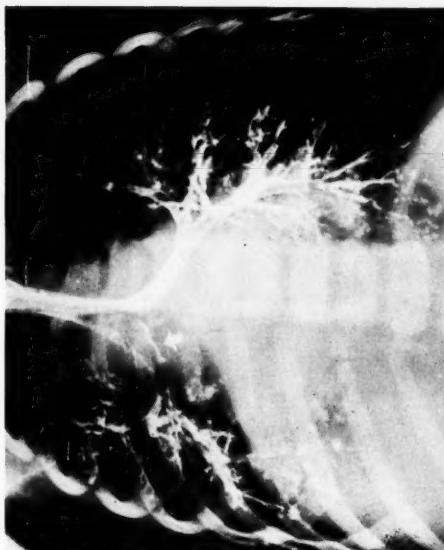


FIG. 2. Case 2, D.D., aged 2 years and 4 months (August 1949), clinically fairly well but still with a slight cough. Bronchogram showing an irregular filling defect of the right bronchus, emphysema of the right upper lobe, and persisting collapse of the right lower and middle lobes. Bronchoscopy examination showed occlusion of the right bronchus by watery-looking granulation tissue; tuberculous pus was aspirated distal to the granulation tissue.



FIG. 1. Case 2, D.D., aged 15 months; cough and wheezing for one month. X-ray, July 1948, showing collapse of the right lower and middle lobes, and mediastinal shift to the right. Bronchoscopic examination showed the right bronchial lumen below the upper-lobe orifice reduced to a slit by bulging of the bronchial walls.

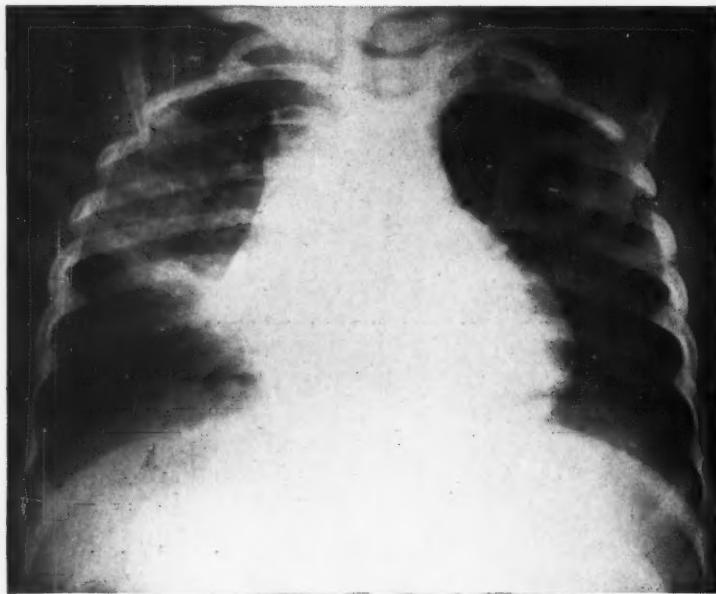


FIG. 4. Case 3, D.T., aged 20 months, October 1943. Collapse of the right middle lobe, mottling in the right upper lobe, emphysema in the right lower lobe, and shift of the mediastinum to the right.

Bronchoscopic examination showed gross narrowing of the right bronchus from bulging of the lateral wall, with partial occlusion of the right upper-lobe orifice

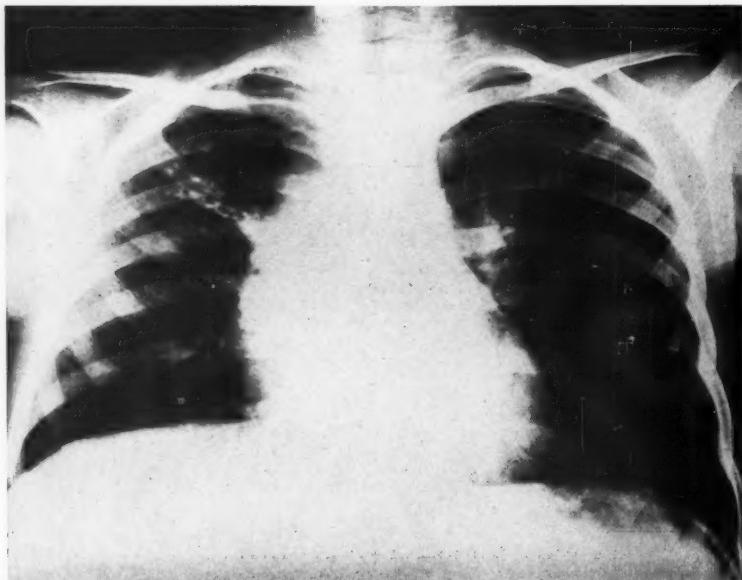


FIG. 5. Case 3, D.T., aged 8½ years, July 1950. Streaking and scattered calcification in the anterior segment of the right upper lobe, and slight shift of the mediastinum to the right.

Bronchoscopic examination showed moderate stricture of the right bronchus. There had been no symptoms referable to the chest lesion for the past 6½ years

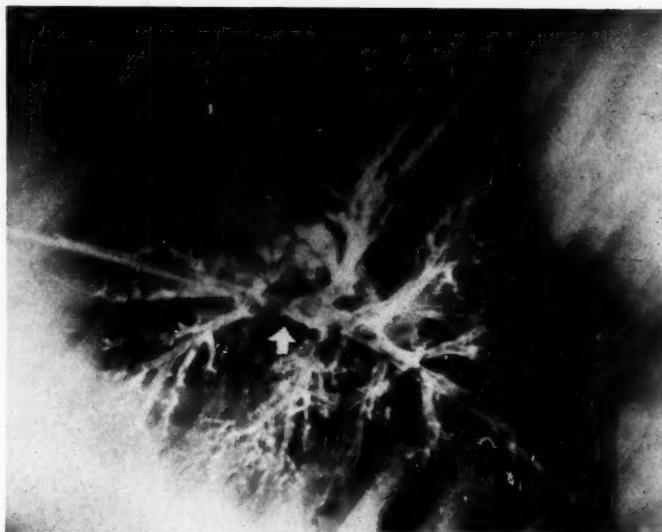


FIG. 7. Case 3, D.T., aged 81 years. Lateral view showing stricture of the right bronchus, and incomplete filling and dilatation of the anterior segment of the right upper lobe and the medial segment of the middle lobe

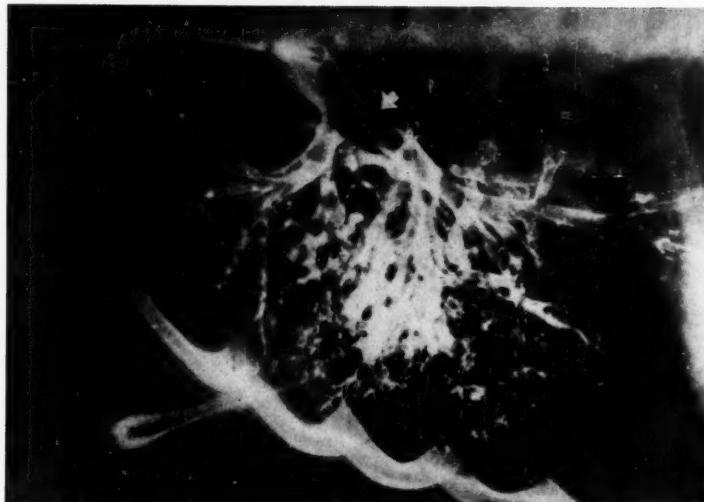


FIG. 6. Case 3, D.T., aged 8½ years. Bronchogram showing stricture of the right bronchus and cylindrical bronchiectasis of the anterior segment of the right upper lobe and the medial segment of the right middle lobe

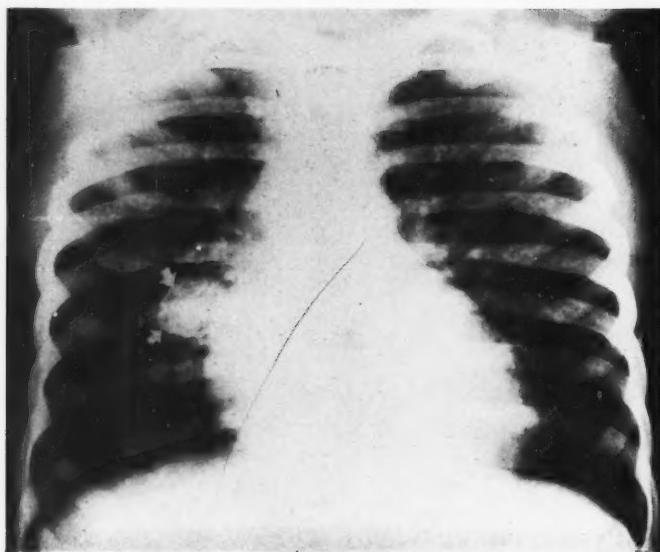


FIG. 8. V.R., aged 4½ years, December 1951. Recurrent colds since the age of 2 years. X-ray showing a large calcified gland in the right hilum and faint opacity of the collapsed right middle lobe.

Bronchoscopy showed a greatly narrowed right bronchus, with a normal upper-lobe orifice; the middle-lobe orifice was seen as a mere slit



FIG. 9. V.R., aged 4½ years, December 1951. Bronchogram showing stenosis of the right bronchus, collapse and complete non-filling of the right middle lobe, and a large calcified gland in juxtaposition to the right bronchus

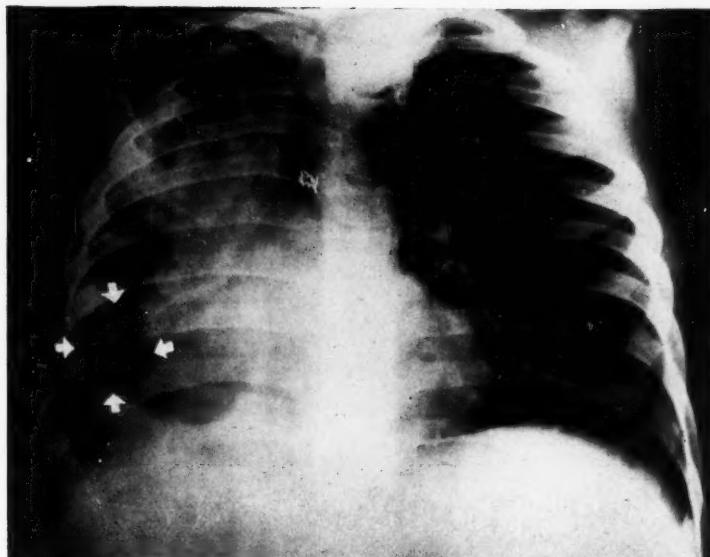


FIG. 10. Case 4, R.S., aged 5 years, October 1948. He had never been ill, and had no symptoms. The chest X-ray showed gross collapse of the right lung, with several large cavities, and gross displacement of the heart and mediastinum to the right.

Bronchoscopy showed stenosis of the right bronchus. A bronchogram showed a grossly retracted right lung, with irregular bronchiectasis of all lobes and several large cavities in the lower lobe



FIG. 11. Case 4, R.S. Operation specimen showing the retracted, fibrotic and bronchiectatic right lung, with right bronchial stenosis and a cavity in the right lower lobe



FIG. 14. O.M., aged 3 years and 10 months, August 1950. Bronchogram showing stenosis of the lingular bronchus and bronchiectasis of the anterior and lingular segments. This lesion developed after collapse of these segments due to tuberculous involvement of the left upper-lobe bronchus at the age of 20 months. Resolution, as judged by routine röntgenograms, was considered complete

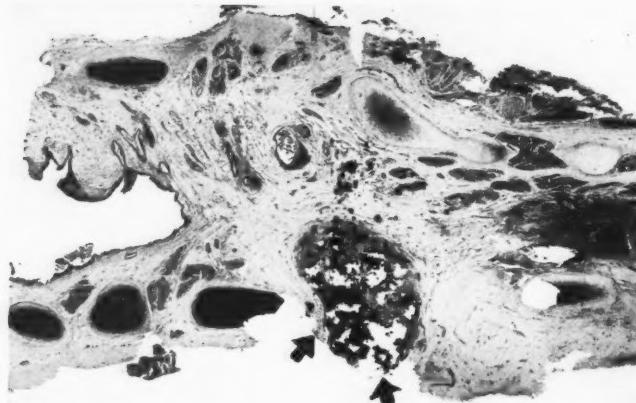


FIG. 13. Longitudinal section through bronchus (Fig. 12) at the level of the stricture ($\times 7$). Arrows indicate calcified amorphous material surrounded by fibrous tissue in the bronchial wall

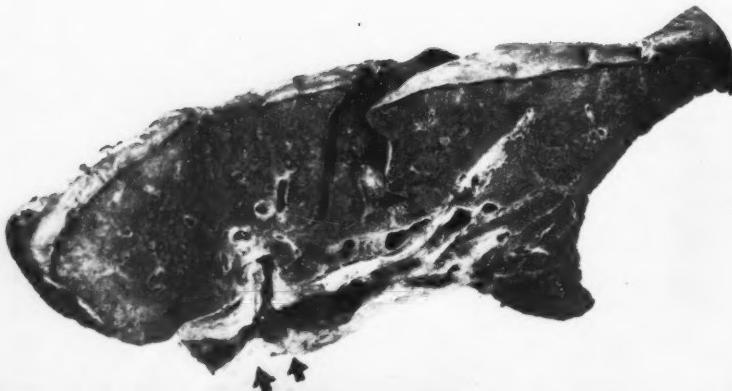


FIG. 12. Operation specimen showing a stricture of the right main bronchus with a healed tuberculous granuloma in the bronchial wall, and a collapsed bronchiectatic right middle lobe. The patient was aged 3½ years, with a history of cough and wheezing at the age of 4 months from tuberculous infiltration of the right bronchus. Healing left a symptomless residual bronchial fistulae

THE ANAEMIA OF ADULT SCURVY¹

By B. BRONTE-STEWART

(From the Department of Medicine, University of Cape Town,
and
Groote Schuur Hospital, Cape Town)

Is vitamin C necessary for erythropoiesis? No convincing answer to this question exists today, yet scurvy dates back to Biblical times, and it is now 20 years since pure synthetic ascorbic acid became available. Experimentally, anaemia has and has not been produced in the susceptible guinea-pig; clinically, anaemia has and has not been observed in manifest human scurvy. The latest reviews of this aspect of ascorbic-acid metabolism (Cartwright, 1947; Tötterman, 1949; Shafar, 1949) reflect this confusion. It is the purpose of the present report to show that anaemia is frequently seen in adult human scurvy, and that the anaemia, no matter how severe, responds promptly and completely to synthetic ascorbic acid.

Patients Investigated and Methods

Thirty-two adults, admitted to Groote Schuur Hospital from 1946 to 1950 with the diagnosis of scurvy, were studied. All had clinically obvious scurvy, usually of a severe degree. Coexisting deficiencies or other diseases were surprisingly rare. All were men ranging in age from 22 to 60 years, with the mean at 36½ years. All but one were Bantus. One (Case 13) died from coronary thrombosis soon after admission. Thirteen patients admitted consecutively (Cases 1 to 13) were subjected to an intensive analysis. The other patients were used merely to determine the incidence and severity of anaemia in adult scurvy, and were treated on admission with synthetic ascorbic acid added to the full mixed hospital diet. With respect to Cases 1 to 13 the following procedure was adopted. Great care was taken that no unprescribed ascorbic acid reached the patient. Each patient was given the diet on which he developed the disease. This was facilitated by the fact that all had consumed a similar diet, the staple diet of the Bantu in South Africa. It consisted of mealie-meal (maize) porridge without milk or sugar, 'stamped' mealies, bread without butter or jam, and black tea or coffee. Its vitamin-C content was zero. Protein 60 gm., fat 20 gm., carbohydrate 356 gm., iron 22 mg., aneurin 1.2 mg., riboflavin 0.65 mg., nicotinic acid 15 mg., and 1,850 calories constituted the average daily intake (Fox and Golberg, 1944). Variable preliminary control periods were instituted. Cases 1 and 4 received ascorbic acid within 24 hours of admission. Otherwise the shortest control period was two days (Cases 2 and 3). The other patients had control periods varying from four to 30 days. During this time Cases 6, 8,

¹ Received January 5, 1953.

and 9 received parenteral vitamin B₁₂ in 30- μ g. doses daily for four days, oral folic acid in 15-mg. doses daily for five days, 400 to 500 mg. of intravenous iron divided over five days, and parenteral vitamin-B complex. Sufficient time was allowed between each of the above drugs to observe any haematological response. Unless otherwise indicated, the usual dose of ascorbic acid at the end of the control period was 1,000 mg. daily given intravenously, as saturation requirements were being tested at the same time by the method of Wright and Lilienfeld (1936). The ordinary full hospital diet was not allowed until the packed cell volume had passed 40 per cent. All patients remained in bed until pronounced cured except Case 5, who was ambulant as soon as ascorbic-acid therapy had started, and Case 12, who remained ambulant throughout. Full haematological investigations were performed according to the standard methods either daily or on alternate days. The bone-marrow from the iliac crest (Rubinstein, 1948) was studied in most cases initially and about two weeks after vitamin-C therapy had begun. In a few patients (Cases 6, 8, and 9), who were subjected to prolonged control periods, examinations were repeated weekly to assess the effect of vitamin B₁₂, folic acid, and other substances, on the bone-marrow. The orthotolidine method (Budtz-Olsen, 1951) was used for the estimation of plasma-iron and total iron-binding capacity. Urinary and faecal urobilinogen excretion was measured by the petroleum-ether method of Watson (1936, 1937) and Schwartz, Sborov, and Watson (1944), and on certain occasions the simplified method of Maclagan (1946) was used to compute the daily faecal excretion from the four-day collection. The standard methods were used for fractional test meals with histamine stimulation, Price-Jones curves (Whitby and Britton, 1942), other haematological investigations (Wintrobe, 1946; Quick, Stanley-Brown, and Bancroft, 1935), serum-bilirubin (Malloy and Evelyn, 1937), and serum-protein pattern determinations (Wolfson, Cohn, Calvary, and Ichiba, 1948; Maclagan, 1944 *a, b*).

Results

The incidence and severity of anaemia in adult scurvy. The normal haematological standards for the adult Bantu man agree well with the normal figures acceptable in races of European origin (Bronte-Stewart and Hickley, 1953). The main haematological findings in all the patients, on their admission to hospital, are given in Table I. The Table shows that anaemia is common in adult scurvy. In over 80 per cent. of these consecutive patients the packed cell volume was below 40 per cent. It also shows that the anaemia in the majority was severe, the lowest recorded figure for the packed cell volume being 8 per cent. Most of the patients who were not anaemic showed the milder degrees of scurvy. One patient (Case 10) had been admitted for the second time. On his previous admission (Case 14) he was not anaemic, but the duration of his complaints was much shorter. In the few patients who were observed for prolonged control periods the anaemia grew worse. It was our impression that the degree of anaemia was proportional to the severity of the scurvy and to the duration of the lack of vitamin C.

The morphology of the anaemia. The anaemia in most cases was normocytic and normochromic, as shown by the mean cell-volumes and haemoglobin

TABLE I
Haematological State on Admission

Only six of the 32 patients had a packed cell volume greater than 40 per cent.

Case number	Red cells (millions/c.mm.)	Haemoglobin (gm./100 ml.)	Packed cell volume (%)	White cells per c.mm.	Case number	Red cells (millions/c.mm.)	Haemoglobin (gm./100 ml.)	Packed cell volume (%)	White cells per c.mm.
1	1.5	4.6	14	3,400	17	2.1	5.2	17	4,280
2	3.9	14	37	7,040	18	3.6	11	31	7,200
3	2.0	6	20	8,600	19	3.9	12	39	3,600
4	2.2	7	23	6,500	20	2.8	8.5	26	3,920
5	2.7	8.2	22	12,200	21	1.7	5	14	2,200
6	1.8	5.4	15	3,900	22	1.5	5	17	8,360
7	6.3	18	59	7,150	23	2.8	7.5	24	4,550
8	2.7	7.3	23	7,200	24	2.2	7.5	25	8,960
9	2.8	7.3	23	8,150	25	0.8	4	8	2,750
10	2.8	8.6	26	7,600	26	1.0	4	12	2,900
11	4.3	13.6	42	6,700	27	1.8	5	15	4,250
12	2.9	8.8	27	6,000	28	3.5	9.4	28	3,950
13	1.5	4.6	15	6,200	29	1.6	4.7	14	6,700
14	5.3	16	51	8,880	30	2.8	8	26	5,600
15	4.7	14	42	5,900	31	4.3	15	41	6,650
16	5.3	14	45	6,150	32	4.0	12	38	4,500

TABLE II

The Initial Haematological Indices, with the Mean Cell-Diameter Measurement and Standard Deviation, in relation to the Severity of the Anaemia

A normocytic normochromic anaemia is the rule, with a tendency to macrocytosis and gross anisocytosis in the severer cases. The reticulocyte count on admission bears no constant relationship to the severity of the anaemia.

Case number	Packed cell volume (%)	Reticulocytes	Mean cell-volume (μ)	Mean cell-haemoglobin concentration (%)	Mean cell-haemoglobin (pg.)	Mean cell-diameter (μ)	Diameter/thickness ratio
1	14	1.2	94.0	33.0	30.9	8.50 ± 0.87	4.7
2	37	2.0	94.8	37.9	35.9
3	20	1.0	101.2	30.0	30.3
4	23	8.0	106.0	30.2	31.8	7.97 ± 0.69	3.8
5	22	1.5	81.2	36.8	30.0
6	15	4.1	82.0	36.0	30.0	6.92 ± 0.69	3.2
8	23	7.4	84.0	32.4	27.0	7.18 ± 0.70	3.5
9	23	1.6	81.4	32.0	26.0	7.31 ± 0.52	3.8
10	26	3.3	94.2	33.0	31.0	7.59 ± 0.62	3.7
11	42	1.4	96.5	32.8	31.6	7.34 ± 0.48	3.2
12	27	1.6	93.1	32.6	30.0	7.36 ± 0.48	3.4
13	15	7.0	100.0	30.6	30.6	7.70 ± 0.89	3.6

indices in Table II. Among the severer cases of anaemia, macrocytic figures are seen in three (Cases 1, 4, and 13); in a fourth (Case 3) the mean cell-volume was increased, but no confirmation was made by a measurement of mean cell-diameter. In only one case, the most severe anaemia of the series (Case 1), was the bone-marrow megaloblastic. Poikilocytosis was rare, but the severer cases presented the more outstanding examples of anisocytosis, a feature which was also noticeable in their Price-Jones curves. In these severe cases marked variation was also seen in the haemoglobin-content of the red cells. Gross hypochromia was not a feature. The initial reticulocyte count was above normal in five cases (Table II); it had no constant relation to the severity of the anaemia. A constant feature, however, where the anaemia was severe enough, was a rise in the reticulocyte level following rest in bed, whether the count was normal initially or not. In three cases normoblasts were seen in the peripheral blood smear. Only one patient of the series (Case 5), admitted with epistaxis, bled externally. His initial white-cell count was slightly raised. In the other cases the white-cell counts were normal or low. In the patients who were studied for long control periods the white-cell count fell slowly until ascorbic acid was given. Normal numbers of platelets were seen in all the cases studied, and the bleeding, coagulation, and prothrombin times were normal.

The bone-marrow in adult scurvy. With the exception of Cases 2, 7, and 11, who were the least anaemic of the 13 patients in the series, the bone-marrow in all cases showed a similar picture of intense hypercellularity. The more severe the anaemia, the greater was this hypercellularity and the more primitive the predominant cell. The marrow was megaloblastic only in Case 1, although in many cases megaloblastoid forms were seen. The white-cell series appeared normal. When marrow examinations were repeated throughout the control periods there was no significant alteration, in spite of the use of other haematinics such as iron, folic acid, and vitamin B₁₂. At the peak of the reticulocytosis which followed vitamin-C therapy the clumps or 'nests' of normoblasts which were seen prior to treatment were equally prevalent, but this similarity applied only to the degree of cellularity. Prior to treatment mitotic figures were rarely seen in these 'nests', and, when obvious, were in telophase, representing (Leitner, 1949) the 'lag' karyokinetic curve of decreased mitosis. The appearance was of numerous cells lying dormant. At the peak of the reticulocytosis, however, the marrow presented the picture of intense activity. Mitotic figures were frequently seen in the 'nests' with the prophase and metaphase predominating. Examinations performed two weeks after ascorbic-acid therapy had begun gave results indistinguishable from normal in all patients, whether iron, folic acid, or vitamin B₁₂ had or had not been given previously.

Gastric juice. Fractional test meals showed a histamine-fast achlorhydria in seven (Cases 1, 2, 3, 5, 6, 8, and 9) and hypochlorhydria in three (Cases 4, 11, and 13) of the 12 patients studied. Peptic activity was present in each case.

Plasma-iron was estimated in seven patients (Case 6, and Cases 8 to 13). In all it varied between 18 and 56 µg. per 100 ml. The total iron-binding capacity was also very low. In Case 11 the levels of plasma-iron (28 µg. per 100 ml.)

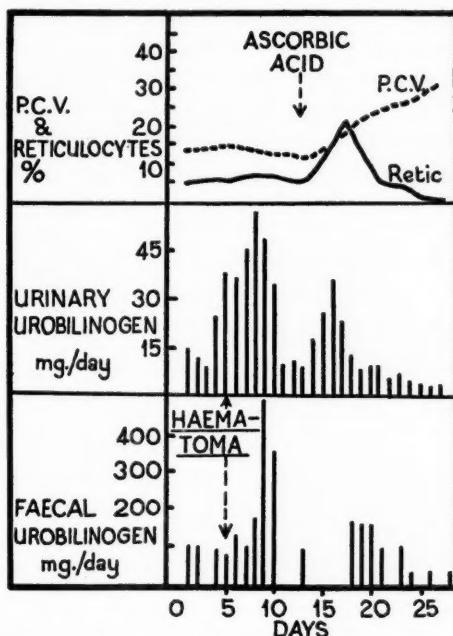


FIG. 1. Case 6. A capillary fragility test caused haematomata in the forearm. An increased urobilinogen excretion followed, but the reticulocytes and packed cell volume (P.C.V.) remained unchanged until ascorbic acid was given.

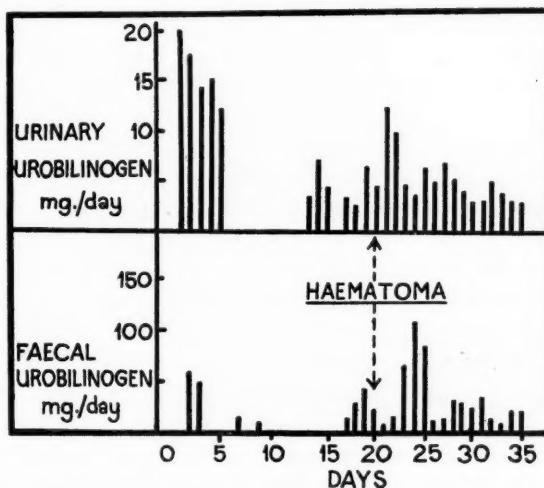


FIG. 2. Case 7. A case of scurvy without anaemia and without haematomata. The intramuscular injection of only 40 ml. of the patient's own blood resulted in an increased urobilinogen excretion.

and total iron-binding capacity (54 µg. per 100 ml.) were among the lowest found, yet the packed cell volume was 42 per cent. The outstanding feature common to these seven patients was the presence of one or more intramuscular haematomata. Unfortunately no anaemic patient who had scurvy without haematomata was available for study. In Case 8 the plasma-iron dropped from 44 µg. to 18 µg. per 100 ml. after the degree of haematoma-formation was

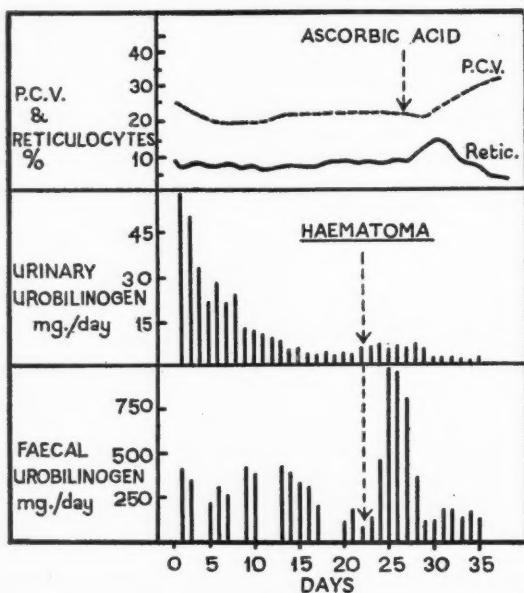


FIG. 3. Case 8. Deliberate haematoma-production, and the effect on the urobilinogen excretion and the anaemia. In this case no 'spill-over' into the urine occurred.

increased with a positive pressure cuff, yet no significant deterioration of the anaemic state followed. In two patients (Cases 10 and 12), to whom ascorbic acid was given soon after admission, the blood picture reached normal figures with the plasma-iron still low and the haematomata still palpable.

Urobilinogen excretion. With rest in bed there was a gradual fall in the urinary urobilinogen excretion, often to normal or nearly normal levels. This decrease was not seen in the faecal levels. Their fall lagged far behind that of the urinary levels, and in patients who received ascorbic acid soon after admission the faecal urobilinogen remained high for some time after treatment had begun. In the first patient studied (Case 6) it was noticed during the phase preceding treatment that the urinary urobilinogen began to increase, and a rise in the faecal urobilinogen soon followed, but no change in the reticulocytes, packed cell volume, or white-cell count took place (Fig. 1). The day before this increase, however, large haematomata had appeared while capillary fragility was being tested with the positive-pressure-cuff method of Wright and Lilien-

feld (1936). A non-anaemic scorbutic patient (Case 7), who had no deep haematoma, but much urobilinogenuria and other signs of grossly defective liver function, was subjected to the same manœuvre of positive pressure with a blood-pressure cuff. As no haematoma resulted, 40 ml. of blood drawn from his vein was injected into his buttock. Even with this small amount of blood there was an immediate rise in the urinary urobilinogen level, followed later

TABLE III

The Relation between the Degree of Anaemia, the Urobilinogen Excretion, and the Extent of Haematoma-Formation on Admission

The normal range of faecal urobilinogen in 30 controls in the present series was from 16 mg. to 175 mg. per day; 83 per cent. of the estimations fell between 25 mg. and 100 mg. per day.

Case number	Packed cell volume (%)	Serum-bilirubin (mg./100 ml.)	Urobilinogen (mg./day)		Extent of haematomata
			Urinary	Faecal	
6	13	0	57.0	490	+++
7	53	0.5	19.6	57	Nil
8	22	0	59.9	390	++
9	23	0	21.2	328	++
10	26	0	15.8	303	++
11	42	1	20.8	310	++
12	27	0	13.5	125	+
13	15	0	63.0	510	++

by a rise in the faecal level, although the latter still remained within normal limits (Fig. 2). When the urobilinogen levels had settled, the small venesection was repeated but the blood was not injected, and no change occurred in the urobilinogen excretion. The fall in urinary urobilinogen with rest in bed, which was noted in all the patients, was allowed to reach normal or nearly normal levels in two other patients (Cases 8 and 9). Positive-pressure cuffs were then applied. In Case 8 the haematoma of the calf, which had decreased considerably in size, then became much larger and more painful. No significant change in the urinary urobilinogen excretion followed, but the faecal urobilinogen rapidly increased to more than 800 mg. per day. There was no change in the already elevated reticulocyte count, and the packed cell volume remained at 23 per cent. (Fig. 3). In Case 9 no haematoma resulted from the positive pressure. No change in urobilinogen excretion or in the haematological picture followed. Towards the end of the control period in this patient, the packed cell volume dropped fairly rapidly from 23 per cent. to 17.5 per cent., but the faecal urobilinogen excretion remained well within normal limits. The haematoma at this stage was barely palpable. From Table III, in which the urobilinogen level is compared with the blood state and the extent of haematoma-formation on admission, it will be seen that a high faecal urobilinogen level was found in a non-anaemic scorbutic patient with a large haematoma (Case 11). In another non-anaemic scorbutic patient who had no haematoma (Case 7) low levels were found. No anaemic scorbutic patient without haematoma was available

for study. Only one patient showed bilirubinaemia (Case 2). In this case both bile and urobilin were present in the urine.

The effect of therapy. Ten anaemic patients (Cases 1 to 6, 8 to 10, and 12) were available for study of the haematological progress.

Rest in bed. In all cases an improvement in the scorbutic state followed. No further bleeding was evident, and the haematomata slowly disappeared. Where

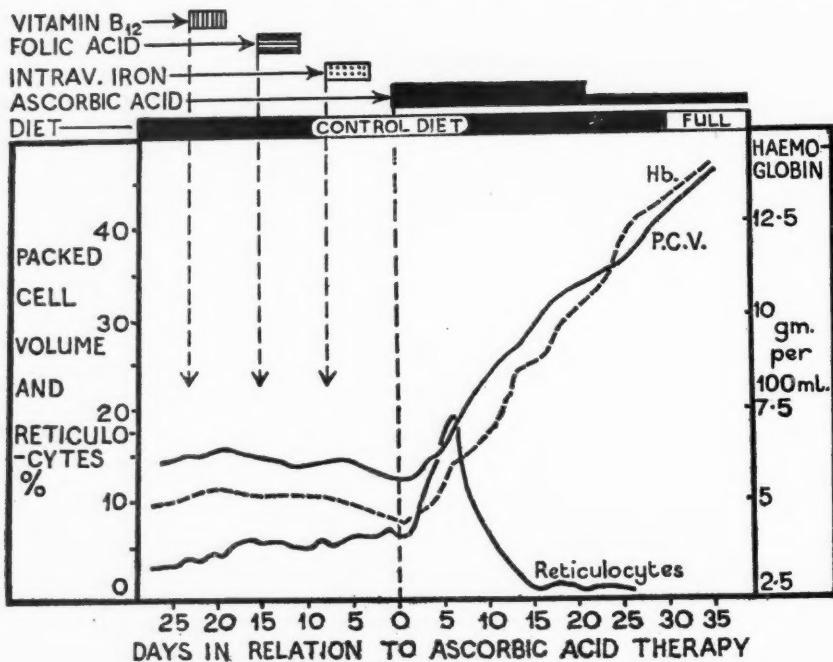


FIG. 4. Case 6. Vitamin B₁₂, folic acid, and intravenous iron had no effect during the control period. There was an immediate response to synthetic ascorbic acid. The original diet was not changed until the packed cell volume (P.C.V.) reached 40 per cent.

the anaemia was severe the reticulocytes increased. In three patients (Cases 5, 6, and 9) a rise in the packed cell volume followed, but in two of these, in spite of a persistently raised reticulocyte count, the anaemia subsequently deteriorated. The third patient (Case 5) was the only one in whom obvious external bleeding could have contributed to the anaemia. His initial complaint was epistaxis. During the 10-day period prior to ascorbic acid therapy his packed cell volume rose by 4 per cent., but in the 10 following days it increased by 12.5 per cent. In this case the beneficial effect of ascorbic acid is graphically shown in Fig. 6.

Haemopoietic and other agents. In the three patients subjected to prolonged control periods (Cases 6, 8, and 9) neither vitamin B₁₂ nor folic acid had any effect on the peripheral blood, bone-marrow, or clinical features (Figs. 4 and 5). In the first five patients (Cases 1 to 5) no iron, additional to that present in the

diet on which the disease developed, was necessary to complete the haematological response that followed ascorbic-acid therapy. The other five anaemic patients (Cases 6, 8, 9, 10, and 12) received iron additional to that present in the diet. Iron was given intravenously to counteract any defective absorption that might be due to scurvy. In Cases 6, 9, 10, and 12 it was given during the control period prior to ascorbic-acid therapy. No effect was seen, either direct

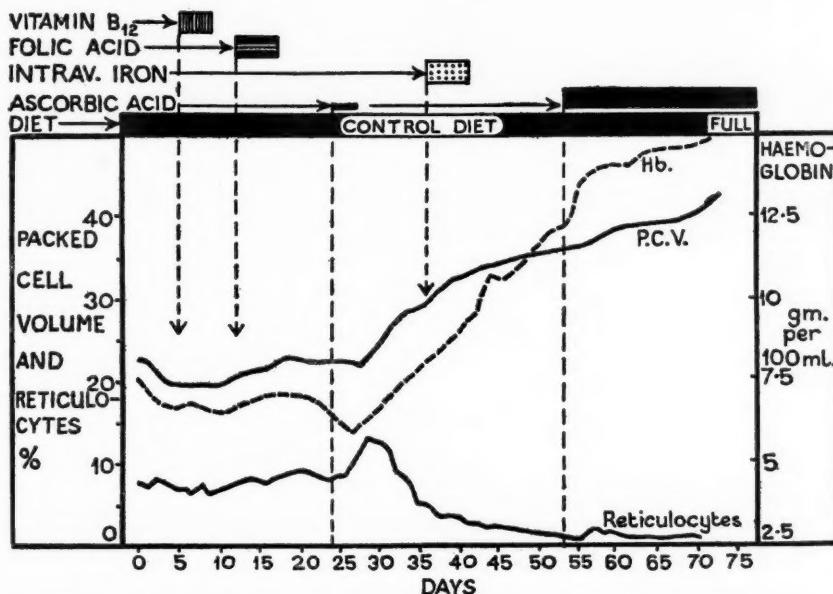


FIG. 5. Case 8. No double reticulocyte response occurred when iron was given after a small dose of ascorbic acid. Further ascorbic acid had to be given for full haematological remission.

or indirect, through hastening the subsequent response to ascorbic acid (Fig. 4). Parenteral iron was given to one patient (Case 8) after a small oral dose of ascorbic acid. No double reticulocyte response occurred; in fact, the rapid response to the oral ascorbic acid slowed down, and full regeneration did not occur until further ascorbic acid was given (Fig. 5). Other agents used were parenteral vitamin-B complex (six cases), penicillin (10,000 units daily) sucked in lozenge form (four cases), and parenteral streptomycin (1 gm. daily for 10 days) with oral succinylsulphathiazole (one case). No effect on the anaemia was seen. In one patient seen subsequently to the present series adrenocorticotrophic hormone, in one dose of 25 mg., led to epistaxis so alarming that blood transfusion and ascorbic acid had to be given immediately.

Ascorbic acid. The synthetic ascorbic acid used in the present investigation was found to have no effect on anaemia resulting from other causes such as infection, malignant disease, or iron deficiency, or on pernicious anaemia in relapse. In the present series of 32 cases of adult scurvy, no anaemic patient

failed to respond rapidly and completely to synthetic ascorbic acid. Except one patient, Case 25, who received blood transfusions, Cases 14 to 32 received no haemopoietic agents other than those that may be present in a full mixed

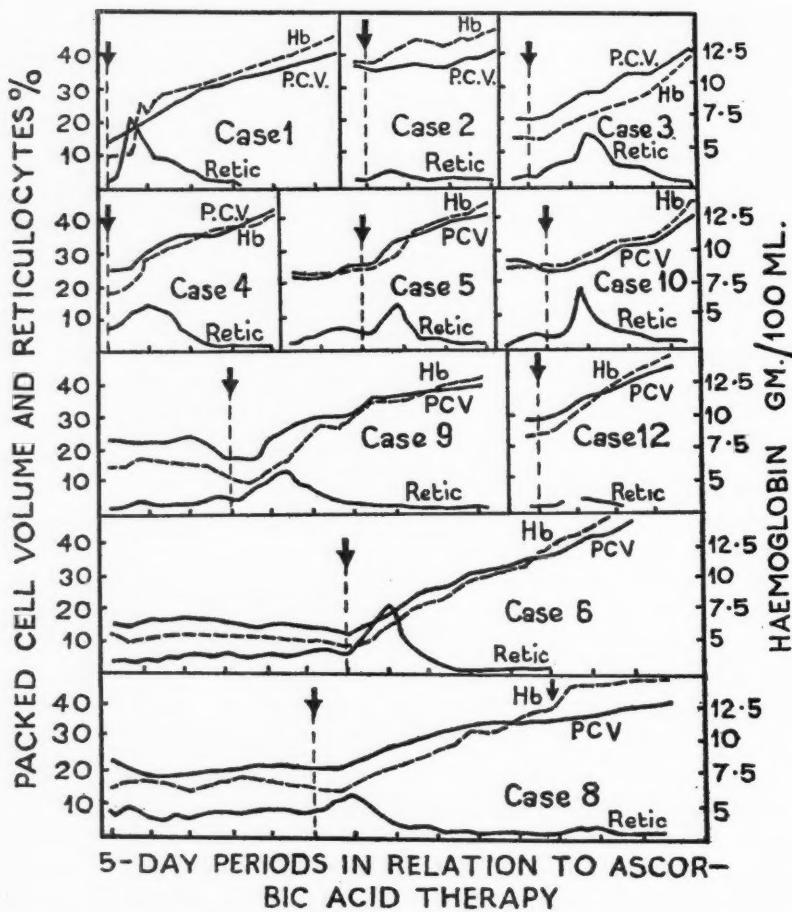


FIG. 6. No patient failed to respond promptly and completely when synthetic ascorbic acid was added (indicated by arrow) to the diet on which the disease developed.

hospital diet. It was possible, therefore, that other deficient factors were supplied in this diet. As regards Cases 1 to 12, whose original dietary environment remained unchanged, the results in the anaemic patients are illustrated graphically in Fig. 6. Where the anaemia was severe enough a prompt reticulocytosis, reaching its peak between the fourth and sixth day, followed ascorbic-acid therapy. In every case a complete and rapid haematological recovery was seen; no other factor such as adequate protein intake, iron, folic acid, or vitamin B_{12} , was necessary before, during, or after ascorbic acid therapy, whether these

factors were deficient at the same time or not. The response appeared to be no less rapid in the two patients who became ambulant at the onset of ascorbic acid therapy (Cases 5 and 12). The fact must be emphasized again that this response occurred without any alteration of the basic environment. The mixed hospital diet was given, in Cases 1 to 12, only after the packed cell volume had reached normal figures.

Discussion

Those who feel that vitamin C is not an essential factor in erythropoiesis have brought forward many points which bear discussion. Recent investigations have shed light on many of these points. Aron (1939) and Sigal (1939) have shown that the inconstancy with which anaemia appears in the scorbutic guinea-pig is due to the size and age of the animal. Animals below 500 gm. in weight are liable to die from infection before the onset of anaemia, which is the last feature to develop in the scorbutic syndrome. Jennings and Glazebrook (1938) suggested that a similar trend in the development of the full scorbutic syndrome exists in man. The results obtained in the present series of patients agree with this suggestion. The presence or absence of anaemia in a given case of scurvy would then depend on its severity. This view would invalidate the approach of Croft and Snorf (1939), Liu, Chu, Yu, Hsu, and Cheng (1941), Lozner (1941), and Schulze and Morgan (1946), who tested the effect of ascorbic acid on an anaemia associated with a biochemically low ascorbic-acid status. In many of their subjects clinical evidence of scurvy was not present. Subsequently it was shown in experimental human scurvy (Medical Research Council, 1948) that the ascorbic-acid content of the white-cell-platelet layer, which provides the most reliable biochemical test, could be zero for as long as 40 days before follicular hyperkeratosis appeared. The absence of any ill health during the pre-clinical phase, and the fact that the minimum daily requirement of ascorbic acid lay in the region of 10 mg., were two further points established in this experiment.

The failure to produce anaemia in experimental human scurvy has been one of the strongest arguments used against the erythropoietic function of vitamin C in the organism. In no case, however, was the severe stage of scurvy reached. Considerations of wound healing (Crandon, Lund, and Dill, 1940) and certain unpleasant cardiovascular effects (Medical Research Council, 1948) terminated these experiments. Even the loss of six litres of blood during the control period (Crandon, Lund, and Dill, 1940), without the development of anaemia, is no argument against a specific influence of vitamin C on the erythron. From the evidence that has so far accumulated, both in the guinea-pig and man, it would appear that at this early stage of scurvy the erythron is functioning normally. When Ungleay (1938) reported a spontaneous reticulocytosis and haematological remission in a scorbutic patient taking a diet low in vitamin-C content, a train of reports appeared disclaiming the specificity of vitamin C in the anaemia of adult scurvy. The absence of deterioration of the anaemia during prolonged control periods in bed, with a diet low in vitamin C, led to similar conclusions

by Ralli and Sherry (1941). It is noteworthy that prior to 1938 the specificity of vitamin C in this form of anaemia had been accepted. This was due to the confirmation of the beneficial effect of orange juice (Shattuck, 1928; Mettler, Minot, and Townsend, 1930; Nisenson and Cohen, 1937; Young, 1938) by the use of synthetic ascorbic acid (Vaughan, 1934; Dunlop and Scarborough, 1935; Jennings and Glazebrook, 1938). Apparently the control diets used by Ungley and by Ralli and Sherry were not completely devoid of vitamin C. In view of subsequent information as to the very small daily requirement of the vitamin, such a diet would not provide adequate control. The profound influence of the metabolic demand on the clinical features of scurvy was not widely known at that time. The resolution of the haemorrhagic manifestations of scurvy during rest in bed, and their reappearance when the patient was made ambulant, were illustrated clearly by Schultzer (1936, 1937), Vilter, Woolford, and Spies (1946), and Brown (1951). There is reason to believe that even in the severer stages of scurvy the tissues are never completely depleted of vitamin C (Pirani, 1952). Considering the small daily requirement, and the fact that rest in bed will release more vitamin C for erythropoiesis, it is reasonable to expect some haematological remission when the patient is kept in bed. The necessity of a preliminary period of rest in bed, before any other measures are tried, now becomes obvious.

Scurvy is a disease resulting from a dietary deficiency. Anaemia itself may result from deficient factors in the diet. The deficiency may depend on the increased demand for vitamin C caused by infection or other diseases, and such diseases by themselves may be potent causes of an associated anaemia. With such complex possibilities, controlled experiment is impossible if the environment in which the disease developed and flourished is altered. An adequate diet, and even a diet lacking in vitamin C, may allow the surreptitious treatment of a combined deficiency, whereas a severely restricted diet, if continued for prolonged control periods, may allow the development of new deficiencies to distort the haematological picture. A multiple deficiency or diseased state may explain the variable morphology that has been described in the anaemia of adult scurvy. This fact has further confused the issue. Unfortunately confirmation by measurements of the mean cell-diameter is rarely found. Reports on the bone-marrow, or serial bone-marrow studies, in scurvy are also rare. They are available in publications by Harris (1928), Mettler, Minot, and Townsend (1930), Mettler and Chew (1932), Wolbach (1937), Jennings and Glazebrook (1938), Israëls (1943), McMillan and Inglis (1944), Vilter, Woolford, and Spies (1946), May, Sundberg, Schaar, Lowe, and Salmon (1951), and Proehl and May (1952). Hypocellular and hypercellular, normoblastic and megaloblastic bone-marrow pictures have been described. Parsons and Hawksley (1933), Parsons and Smallwood (1935), and Parsons (1938) attempted to explain this variability by a slowing of erythropoiesis which may become disproportionate, while Jennings and Glazebrook (1938) suggested that the macrocytosis is related to the severity of the lack of vitamin C. The latter view receives support from the results seen in the present series, and from Proehl and May (1952), who have recently

shown that a megaloblastic anaemia becomes superimposed as the anaemia of scurvy progresses in monkeys. Undoubtedly age, the quantity of endogenous vitamin C, the severity of the anaemia, and possible complicating deficiencies and diseases are factors to be considered when interpreting these conflicting findings. In some cases the haemorrhagic tendency in scurvy may be responsible for the variable blood picture by producing a superimposed hypochromic anaemia. It has been suggested that the anaemia may be due entirely to this mechanism (Wintrobe, 1946; Proehl and May, 1952), so that the response to ascorbic acid would be due merely to cessation of the loss of blood. Against this view is the observation made by McMillan and Inglis (1944) and Vilter, Woolford, and Spies (1946), that no correlation exists between the extent of ecchymosis or of external loss of blood and the severity of the anaemia. In the patients of the present series who were studied over long control periods, the haematomata slowly disappeared, yet the anaemic state slowly deteriorated. Induction of further bleeding into the tissues with positive-pressure cuffs did not lead to any sudden deterioration of the anaemia. Neither in its morphology nor in its response to iron therapy, nor in the capacity of the plasma to bind iron, did this anaemia resemble that due to chronic loss of blood.

Differentiation, on morphological grounds, of the anaemia of adult human scurvy from the deficiency dyshaemopoietic anaemias can be exceedingly difficult. The appearance of the peripheral blood smear, the leucopenia, the histamine-fast achlorhydria, and the occasionally associated megaloblastic bone-marrow have led to an erroneous diagnosis of pernicious anaemia. Recent studies have focused interest on the relation between folic acid and ascorbic acid in the metabolism of certain aminoacids (Sealock, Perkinson, and Basinski, 1941; Sealock and Lepow, 1948; Woodruff and Darby, 1948; Woodruff, Cherrington, Stockell, and Darby, 1949; Luhby and Wheeler, 1949; Rogers and Gardner, 1949; Morris, Harpur, and Goldbloom, 1950; Vilter, Horrigan, Mueller, Jarrold, Vilter, Hawkins, and Seaman, 1950; May, Nelson, Salmon, Lowe, Lienke, and Sundberg, 1950). In the scorbutic monkey megaloblastic bone-marrow has reverted to normal after the use of folic and folinic acid (Proehl and May, 1952). It is significant, however, that the experimental diet in these monkeys was poor in folic acid, and that the control animals developed anaemia in spite of ascorbic-acid supplements. The latter anaemia, however, was much later in onset than that of the test animals. Thus the exact relationship of this experimental anaemia in scorbutic monkeys to the anaemia of adult human scurvy is uncertain. In the treatment of adult human scurvy, an ordinary hospital diet lacking vitamin C (Vilter, Woolford, and Spies, 1946), with liver supplement (Jennings and Glazebrook, 1938) and with vitamin-C-free liver (Mettier, Minot, and Townsend, 1930) failed to induce a response until vitamin C was given. In the present series neither vitamin B₁₂ nor folic acid was effective in the three patients studied; none of these three, however, had a megaloblastic bone-marrow.

The low plasma-iron levels and the low total iron-binding capacity in the present series seemed to bear a close relationship to the intramuscular

haematomata, and therein showed a state analogous to the experimental anaemia resulting from a sterile intramuscular turpentine abscess, produced in the dog by Cartwright and Wintrobe (1949). Only in this respect, however, were the two forms of anaemia similar. There was no correlation between the presence or severity of the anaemia and either the plasma-iron level or the extent of haematoma-formation. An increase of haematoma-formation by a positive-pressure cuff had no effect on the anaemic state, but a marked rise in the faecal excretion of urobilinogen followed. It appeared that extravascular haemolysis in the haematoma could account for most of the excess in faecal urobilinogen. The absence of bilirubinaemia in these patients is akin to the results obtained by Pass, Schwartz, and Watson (1945) after the intravenous injection of haematin. Proehl and May (1952) have since shown, in the scorbutic monkey, that the increase of faecal urobilinogen coincided with the onset of periorbital haemorrhages and bleeding elsewhere into the tissues. In the present series, therefore, the plasma-iron, total iron-binding capacity, and faecal urobilinogen excretion were of no assistance in determining the mechanism of the anaemia. They appeared to be related to the intramuscular haematoma, which in turn appeared to have no direct relation to the anaemia.

It now seems unlikely that an intravascular haemolytic mechanism can have caused these increases of faecal urobilinogen. Otherwise it would have been an attractive explanation of the inconstant reticulocytosis seen in the severer stages of untreated scurvy, as Vilter, Woolford, and Spies (1946) originally suggested. Vaughan (1934), on the other hand, felt that such reticulocytosis was due to stimulation of the bone-marrow by repeated haemorrhages. In the present series the inconstant reticulocyte level on admission, compared with the constantly elevated level soon after rest in bed was instituted in all cases in which the anaemia was sufficiently severe, might suggest that some endogenous source of vitamin C was stimulating the bone-marrow. There is evidence that such a source exists, since the scorbutic patient is never completely depleted of vitamin C (Pirani, 1952). Through decreasing the demand made by functions such as locomotion, more vitamin C may become available for more vital functions such as erythropoiesis. In the milder cases, as previous reports have shown, this source may be sufficient for full regeneration when the patients are no longer ambulant. Where the body stores are less adequate a state is produced analogous to the slight reticulocytosis, without subsequent haematological remission, found in pernicious anaemia when an inadequate dose of liver has been given (Minot and Castle, 1935). The very small amount of vitamin C necessary both for the cure (Barnes, 1947) and for the prevention (Medical Research Council, 1948) of scurvy fits well with this hypothesis. In the present series of patients, when an exogenous source of vitamin C became available, the picture did not change except in degree. The reticulocytosis became even more marked, and the bone-marrow, although its appearance was similar to that found before treatment, was the scene of intense activity.

From the present study it seems unnecessary to postulate that a combined deficiency is responsible for the anaemia that is found in uncomplicated adult

human scurvy. Anaemia develops and persists in scurvy in spite of adequate supplies of iron, vitamin B₁₂, and folic acid. Of the 26 anaemic patients in the series none failed to respond to synthetic ascorbic acid. In 10 patients whose diet remained unchanged after admission, this response was prompt and complete without any other factor being necessary before, during, or after such treatment.

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APPENDIX

Case Reports

The dietary and environmental history was similar in each case. All were male Bantus from distant rural and somewhat primitive areas. They had migrated to the city for the sole purpose of earning money as rapidly as possible. The money was to be used to buy cattle, which is the index of wealth among the rural Bantu. The cattle, in most instances, provided the traditional 'labola' or marriage fee, so that the quality or number of the proposed wives determined for each man his length of stay in the city. Strict economy was therefore practised. This meant that the cheapest food with the greatest bulk was chosen, regardless of its lack of nourishing qualities. Usually its vitamin-C content was nil. At the same time his preference for over-cooking in an open iron pot over a wood fire would ensure the complete destruction of any remaining trace of vitamin C. So steadfastly did the men follow their purpose that it was not uncommon to hear that they had left an employer who provided a midday meal, because it was thought that more money could be earned from an employer who was not so considerate. Since they were unskilled, their work was in the class of heavy manual labour. Time, as we know it in months and years, means little to the rural Bantu. For this reason the patient's age and the duration of his complaints can only be approximate. All showed the classical features of the scorbutic syndrome: follicular hyperkeratosis, particularly noticeable on the anterior aspect of the thighs and ulnar border of the forearms; perifollicular haemorrhage, which is very difficult to recognize in the black skin; localized or diffuse gingival hyperplasia at the site of dental caries; and certain other features, which will be mentioned in each case. To avoid unnecessary repetition, only the haematological features which are not contained in the text (Tables I to III and Figs. 1 to 6) will be mentioned in the case reports.

Case 1. D. Z., of Nyasa origin, aged 33 years, was admitted with a chronic non-healing ulcer of one month's duration, which had followed continual trauma from a shoe. It was situated just in front of the left medial malleolus. There was a haematoma near the right cubital fossa, and a haematoma of the right thigh. There was a mild pyrexia. The erythrocyte sedimentation rate (Westergren

method, uncorrected) was 60 mm. after the first hour. The serum-bilirubin was 0.5 mg. per 100 ml., and the serum thymol and colloidal gold reactions were normal. Ascorbic acid was given on the first day. The ulcer was completely healed by the 19th day, and two weeks later no signs of scurvy were to be seen.

Case 2. S. N., of Tanganyika origin, aged 47 years, was admitted with a painful haematoma of the left calf of two weeks' duration. A firm spleen was palpable 2 cm. below the costal margin. The erythrocyte sedimentation rate was 8 mm. after the first hour. The serum-bilirubin was 3.2 mg. per 100 ml., and bile and urobilin were present in the urine. The serum-albumin was 4.0 gm. and the serum-globulin 3.9 gm. per 100 ml. The thymol turbidity was 4 units, the thymol flocculation 3, and the serum colloidal gold reaction 4. Ascorbic acid was added to the control diet on the third day; it rapidly cured the anaemia and the scorbutic features, but had no effect on the defective hepatic function and the splenomegaly. No malarial parasites were ever isolated. He had come from a hyperendemic malarial area before migrating to Cape Town three years previously.

Case 3. D. M., of Tanganyika origin, aged 40 years, was admitted with a painful haematoma of the right popliteal fossa and thigh of two weeks' duration. A firm spleen could be felt 2 cm. below the costal margin. The serum-bilirubin, thymol turbidity, and colloidal gold reaction were normal. The serum-albumin was 3.5 gm. and the serum-globulin 2.8 gm. per 100 ml. Urobilin was present in the urine. The erythrocyte sedimentation rate (uncorrected) was 120 mm. after the first hour. Ascorbic acid was given after a three-day control period, and there was a rapid clinical response. The splenomegaly remained unchanged. No malarial parasites were ever isolated. He, too, had come from a hyperendemic malarial area before migrating to Cape Town.

Case 4. J. J., of Xhosa origin, aged 49 years, was admitted with a painful haematoma of the right calf which had lasted one week. There was a serous effusion into the neighbouring knee-joint, and pitting oedema over the anterior aspect of the right leg. The serum-bilirubin and the colloidal gold and thymol reactions were normal. The serum-albumin was 3.8 gm. and the serum-globulin 2.2 gm. per 100 ml. The erythrocyte sedimentation rate (uncorrected) was 60 mm. after the first hour. Ascorbic acid was given on the first day and discontinued on the 20th day, by which time all clinical features had disappeared except the follicular hyperkeratosis, which was just detectable. Vitamin-B complex and full diet caused no further rise in the packed cell volume.

Case 5. J. C., of Xhosa origin, aged 25 years, was admitted with epistaxis of two days' duration. His nostril was plugged, and no further bleeding occurred. The serum-bilirubin was normal, but the serum colloidal gold and thymol reactions were grossly abnormal. The serum-albumin was 3.3 gm. and the serum-globulin 2.6 gm. per 100 ml. The erythrocyte sedimentation rate (uncorrected) was 40 mm. after the first hour. After 10 days ascorbic acid was given and the patient was allowed to get up. Three weeks later the serum-albumin had increased to 4.5 gm. per 100 ml., and acid (14 units) appeared in the stomach after histamine stimulation. The liver-function tests remained grossly abnormal. Vitamin-B complex and full diet caused no further improvement.

Case 6. E. C., of Tanganyika origin, aged 27 years, was admitted after having collapsed three days previously. Seven weeks before, haematomata had appeared in his left forearm after trauma; other haematomata had followed

in the left leg. He had gone to bed, and after two weeks the swellings had subsided. Giddiness and syncope followed the assumption of the erect position. On examination there was pigmentation of the skin overlying a thickening of the underlying muscles at the site of the former swellings. There were splinter haemorrhages of the finger nails, and a firm spleen was palpable 2·5 cm. below the costal margin. No malarial parasites were demonstrable, but he had originated from a hyperendemic malarial area. There was no bilirubinaemia, and the thymol and colloidal gold reactions were normal. The serum-albumin was 4·0 gm. and the serum-globulin 3·0 gm. per 100 ml. The capillary fragility test caused large haematomata in the forearm (page 313, Fig. 1). The erythrocyte sedimentation rate (Westergren, uncorrected) was 126 mm. after the first hour. The mild pyrexia noted on admission rose to 101° F. after the fresh haematomata had appeared. During the control period of approximately 30 days, several haematinic agents were tried without success. The packed cell volume dropped slowly from 15 per cent. to 12·5 per cent., while the reticulocyte percentage remained fairly constant in the region of 7. During this time, in spite of a constant fluid intake, the urinary output steadily lessened, and the liver-function tests showed no change. Penicillin lozenges had no effect on the gingival hyperplasia, but the pain and oral fetor were improved. The pyrexia, urinary output, leucopenia, and erythrocyte sedimentation rate soon reverted to normal after ascorbic-acid therapy. The serum-albumin rose to 4·6 gm., and the serum-globulin dropped to 2·7 gm., per 100 ml. The skin became shiny and less dry, but the follicular hyperkeratosis did not disappear until five weeks later. The pigmented areas gradually faded. The splenomegaly did not change.

Case 7. J. K., of Zulu origin, aged 50 years, was admitted because of progressive weakness and a painful mouth of three weeks' duration. Follicular hyperkeratosis, perifollicular haemorrhages, and gingival hyperplasia were the scorbutic signs, but there were well advanced mental, tongue, and skin signs of vitamin-B complex deficiency. The latter features disappeared promptly when vitamin-B complex was given. Full diet and vitamin C were given five weeks later because, being mildly scorbutic and without anaemia, he acted as a control in the studies of urobilinogen excretion (page 313, Fig. 2). The erythrocyte sedimentation rate remained between 3 mm. and 8 mm. per hour, and the serum-bilirubin, 0·5 mg. per 100 ml., was unchanged at the end of this period. The liver-function tests were grossly abnormal, and remained so. The serum-albumin dropped from 5·3 gm. to 4·6 gm., and the serum-globulin from 3·2 gm. to 2·7 gm., per 100 ml. The packed cell volume fell from 59 per cent. to 53 per cent., and it is possible that the initial figures were due to the slight dehydration noticed on admission. The fractional test meal disclosed no change, free acid being present before and after histamine.

Case 8. Q. S., of Xhosa origin, aged 35 years, was admitted with painful swellings of the left calf and right forearm. The swellings were haematomata. The erythrocyte sedimentation rate (uncorrected) was 60 mm. per hour. The icteric index was 14, but there was no bilirubinaemia, and the thymol and colloidal gold reactions were normal. The serum-albumin rose from 3·4 gm. to 4·1 gm., and the serum-globulin dropped from 2·5 gm. to 1·5 gm., per 100 ml., during the control period. Pyrexia did not disappear until ascorbic acid was given, and the increase in the haematoma after the application of a positive-pressure cuff caused the temperature to rise further. The effect of this manœuvre on the urobilinogen excretion is shown in Fig. 3 (page 314), and the plasma-iron decreased at the same time from 44 µg. to 18 µg. per 100 ml. Nine days later, the fifth day after the first dose of ascorbic acid, it was 56 µg., and

the packed cell volume was 27 per cent., 5 per cent. higher than before treatment. Twenty days after treatment had begun the packed cell volume was 36 per cent., the plasma-iron 86 μg . per 100 ml., and the total iron-binding capacity 393 μg . per 100 ml. Folic acid, vitamin B₁₂, and vitamin-B complex had no effect during the control period of 26 days. No iron was given until the reticulocytosis following three daily oral doses of 100 mg. ascorbic acid had settled. Thirty days later more ascorbic acid had to be given, as the packed cell volume had remained stationary at 36 per cent. for the previous 10 days (page 317, Fig. 5). Full diet was given two weeks later. Seventeen days after the initial ascorbic acid the haematomata were barely palpable, but the colloidal gold reaction and thymol flocculation had become abnormal, and remained abnormal up to the time of discharge from hospital. The achlorhydria remained histamine-fast.

Case 9. F. G., of Nyasa origin, aged 24 years, was admitted with a painful haematoma of the right calf and an effusion of the right knee-joint of two weeks' duration. For four weeks he had difficulty in eating owing to painful, swollen gums, which did not bleed. Just before the onset of his illness he had had an episode of diarrhoea. The uncorrected erythrocyte sedimentation rate was 130 mm. after an hour. There was no bilirubinaemia, but the serum colloidal gold and thymol reactions were abnormal. The serum-albumin was 4.6 gm. and the globulin 2.4 gm. per 100 ml. The plasma-iron was 44 μg . per 100 ml. On a few occasions a small amount of fresh blood was noticed in the stools. Bacteriological examination was negative, and streptomycin with sulphasuccidine had no effect. No blood was seen in the stools after ascorbic-acid therapy. At the end of the 17-day control period the haematomata had almost resolved, but the sulphasuccidine may have contributed towards the low normal levels of faecal urobilinogen at that time. Folic acid, vitamin B₁₂, and intravenous iron had no effect. On the 10th day of the control period the packed cell volume was 1.5 per cent. higher, but a drop of 5 per cent. during the next seven days led to the administration of ascorbic acid. As in Cases 6 and 8, an increased urinary output followed, and the erythrocyte sedimentation rate fell rapidly to normal. The serum colloidal gold and thymol reactions remained abnormal even on a full diet, which was given five weeks after ascorbic-acid therapy had begun. Free gastric acid (6 units) reappeared, and reached 13 units after histamine. The mild pyrexia, as in the other severe cases, reverted to normal after ascorbic acid.

Case 10. E. M., of Pondoland, aged 59 years, was admitted with haematomata of the left calf and arm, and right thigh, of more than three weeks' duration. Two months previously he had noticed painful, swollen gums for the first time. Seven months previously he had been in hospital for 10 days with scorbutic changes in the skin and gums, but no haematomata were palpable. There was no anaemia (Case 14, page 311, Table I). The duration of his complaints at the time of that admission to hospital was only two weeks; during the 10 days in hospital he received 500 mg. ascorbic acid intravenously daily for four days, and 300 mg. by mouth three times daily for the remaining period. According to his dietary history no further vitamin C was consumed for the next seven months. The erythrocyte sedimentation rate (uncorrected) was 68 mm. after the first hour. The serum-albumin was 4.5 gm. and the serum-globulin 2.8 gm. per 100 ml. The serum colloidal gold and thymol reactions were slightly abnormal, and did not change after treatment. There were 7 units of free acid before, and 20 units after, histamine; these amounts increased to 62 units and 78 units three weeks after treatment. There was radiological evidence of healed

pulmonary tuberculosis in the right apical region. Repeated examinations of the sputum were negative. The serum-bilirubin was 0·5 mg. per 100 ml. The plasma-iron and total iron-binding capacity were low. Ascorbic acid was given on the sixth day. Eighteen days later, when the packed cell volume was 41 per cent., full diet was given. An apparent diuretic effect of ascorbic acid was again noticeable, and the mild pyrexia returned to normal. The unusual feature of this case was the failure of the erythrocyte sedimentation rate to return to normal. No cause for this could be found.

Case 11. T. P., of Nyasa origin, aged 27 years, was admitted with a painful haematoma of his right calf of three weeks' duration. There was a mild pyrexia. The serum-bilirubin was 1 mg. per 100 ml., the serum-albumin 2·8 gm., and the serum-globulin 3·7 gm. per 100 ml. After two weeks of ascorbic-acid therapy this ratio was still abnormal (albumin 3·8 gm., globulin 4·2 gm. per 100 ml.). The serum colloidal gold and thymol reactions remained normal throughout. The plasma-iron was 28 μ g. and the total iron-binding capacity 54 μ g. per 100 ml. There was no achlorhydria. There was slow regression of the haematoma after ascorbic-acid therapy, and the plasma-iron level rose slowly to normal figures. The packed cell volume was 46 per cent. on his discharge.

Case 12. G. M., of Xhosa origin, aged 55 years, when first seen had a haematoma of the right calf of one month's duration. He remained ambulant throughout the period of observation. There was no bilirubinaemia; the serum-albumin was 3·7 gm. and the serum-globulin 3·8 gm. per 100 ml. The serum colloidal gold and thymol reactions were normal. The plasma-iron was low. Unfortunately the reticulocytes were not counted between the second and sixth days of ascorbic-acid therapy, but the packed cell volume rose from 27 per cent. to 46 per cent. in only 18 days. The clinical features, in spite of ambulation, rapidly improved.

Summary

1. From a study of 32 cases it appears that anaemia has a high incidence in adult scurvy, and can be very severe.
2. In 10 consecutive cases of adult scurvy with anaemia, a prompt and complete haematological response followed the addition of pure ascorbic acid alone to the diet on which the disease developed. This response occurred without requiring an adequate aminoacid intake, iron, extrinsic factor, or other vitamin before, during, or after vitamin-C therapy, whether these factors were deficient in the diet or not. Folic acid, vitamin B₁₂, and intravenous iron failed to have any influence on the bone-marrow or blood picture, but no patient failed to respond to synthetic ascorbic acid. To the other anaemic patients no known haemopoietic factor, other than that already present in the ordinary hospital diet with added ascorbic acid, was given. In each case a rapid and complete haematological recovery occurred.
3. Morphologically the anaemia is normochromic and normocytic, but occasionally macrocytic in the more severe cases. Variation of the size and haemoglobin-content of the red cells becomes more noticeable as the anaemia progresses. Variation in shape was less frequently seen. Reticulocytes may or may not be present in increased numbers in the severer cases. When rest in bed is instituted this increase is constant.

4. The bone-marrow, although often hypercellular in appearance, shows decreased mitosis. Occasionally megaloblasts are seen. This appearance, with the frequent leucopenia and a histamine-fast achlorhydria, may combine with the above features to simulate other deficiency dyshaemopoietic anaemias of the megaloblastic type. Pepsin activity is normal.

5. Increased excretion of pigment, suggestive of a haemolytic process, was shown to be due to extravascular haemolysis in the haematoma. No correlation existed between the state of anaemia and the fluctuations in pigment excretion.

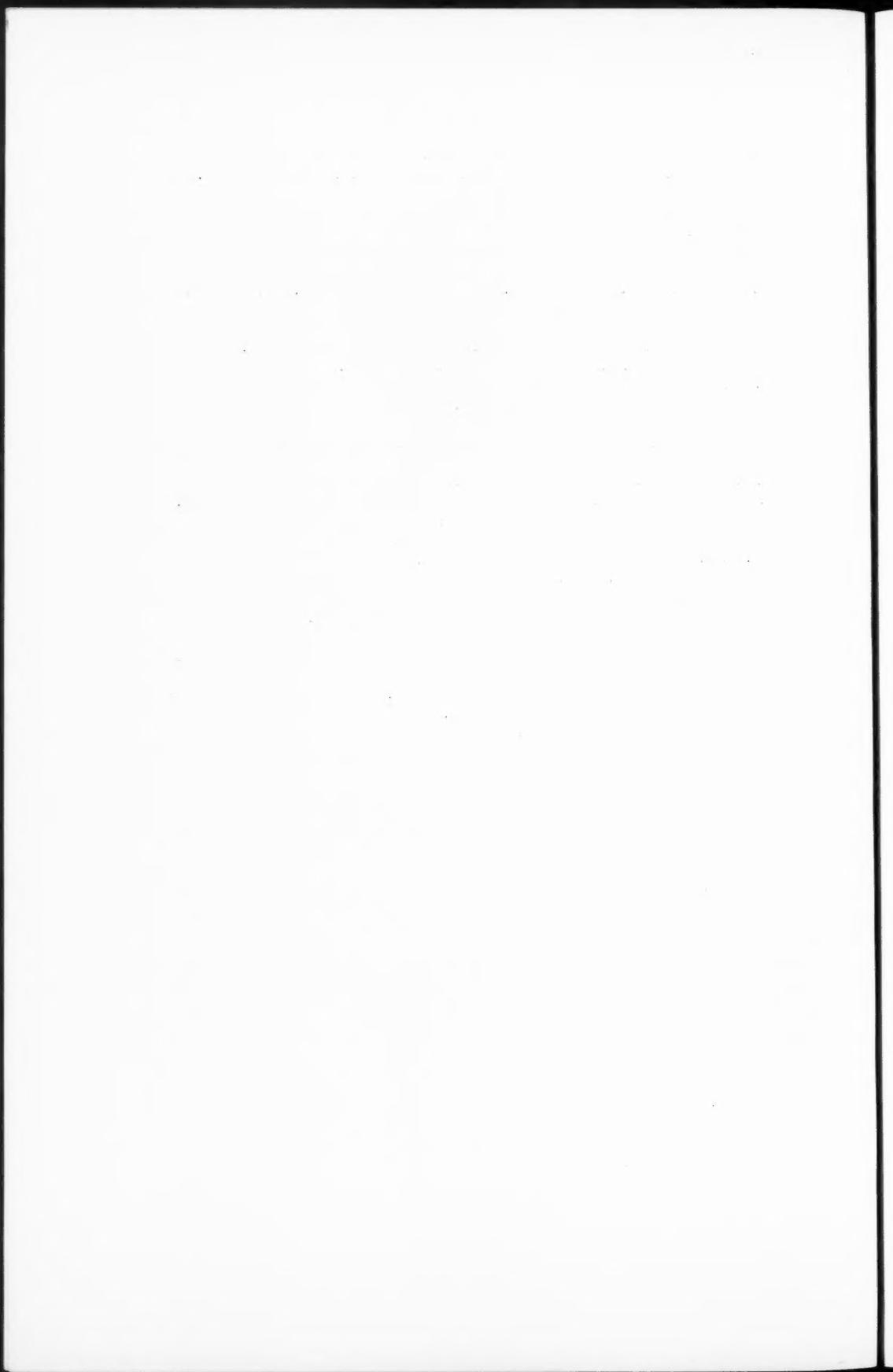
6. The haematoma appeared also to be responsible for the low levels of plasma-iron and iron-binding capacity.

7. It is felt that the conflicting views as to the participation of ascorbic acid in erythropoiesis have been due to the following causes: (1) Ascorbic acid by itself has no proved effect in combating any condition other than scurvy. (2) Both anaemia and scurvy may result from dietary deficiencies, and to prove that one is the result of the other a very strict dietary control is necessary. The simplest, and yet most accurately controlled, diet is probably that on which the disease developed. (3) Lack of vitamin C, when it causes anaemia, is chronic and takes the form of clinically obvious scurvy; it therefore does not mean merely the chemical state of 'unsaturation'. (4) Influences exerted by haemorrhage, by other deficiencies, and by diminished metabolic requirements (such as occur with rest in bed) should be eliminated before the effect of pure synthetic ascorbic acid on erythropoiesis is assessed.

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STUDIES IN GOUT, WITH PARTICULAR REFERENCE TO THE VALUE OF SODIUM SALICYLATE IN TREATMENT¹

By F. G. W. MARSON

(From the Department of Therapeutics, University of Birmingham, General Hospital, Birmingham)

ALTHOUGH accounts of the disease may be found in the earliest medical writings, the importance of uric-acid metabolism in gout was not demonstrated until 1797, when Wollaston showed uric acid to be the principal constituent of the characteristic tophi. In the following year Pearson confirmed this finding, and its significance was enhanced in 1848, when Garrod demonstrated by means of his 'thread test' the presence of increased amounts of uric acid in the blood of gouty patients. The exact pathology of the acute arthritis of gout is unknown, but there is general agreement that deposition of sodium urate in the tissues is the cause of its chronic symptoms. The concentration of uric acid in the body-fluids of gouty persons is constantly high, and sufficient to produce supersaturation and precipitation of uric acid in the form of sodium urate crystals. These deposits act as irritants, and microscopy reveals a surrounding inflammatory and foreign-body reaction (Bauer, 1943). In severe cases joints become disorganized, with destruction of soft tissues, cartilage, and subchondral bone, and on occasions massive urate deposits replace entirely the small bones of the hands and feet. Tophi may ulcerate through the overlying skin. Rarely the disorganization may be so great as to necessitate amputation of fingers, toes, and even limbs. Talbott (1949a) recorded a patient whose continued co-operation in treatment did not prevent either rapid crippling or amputation of a leg at 37 years of age. A radiograph of the left foot at 21 years of age was normal, and yet showed gross structural changes about seven years later. Since urate deposition appears to be the all-important feature of chronic gout, treatment should be directed towards its prevention and aim at maintaining a persistently lowered urate-content of the body-fluids to avert the precipitation of urate crystals. The results recorded later in the present paper show in addition that treatment based on these methods may actually lead to partial reabsorption of deposits of long standing. Theoretically treatment may be directed either to reduction of the rate of uric-acid formation in the body or to the administration of drugs which reduce the reabsorption of urate through the renal tubules. Many attempts at such therapy have been made, but little success has been reported. Thus Talbott (1949b) wrote: 'It may not be surprising that the cure for articular gout has not been discovered, but it is a disappointment to students of the disease that methods have not been devised to reduce the urate-content of the body. It is believed by us that all that would be needed would be a

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means to produce a permanent reduction of the concentration of urate in body fluids. If the urate concentration could be maintained permanently in the normal range, gouty arthritis should never develop.

With reference to the former of these methods, it is clear that uric acid is the end-product of purine metabolism in man, and is derived normally from exogenous and endogenous sources in almost equal proportion. Isotope studies have shown that glycine and ammonia contribute nitrogen to the formation of uric acid, and that carbon atoms are derived from formate, glycine, and carbon dioxide (Shemin, 1950). It thus appears that, in addition to purines, the dietary carbohydrates, fats, and proteins are all potential precursors of uric acid. In spite of the widespread belief that diet is an important causal factor in gout, there has been little controlled investigation into the effects of dietary changes upon serum uric-acid levels. Jacobson (1938) found that the consumption by gouty persons of a purine-free diet did not significantly influence the serum uric-acid level. His investigations covered periods up to three months. Bauer and Klemperer (1944) and Talbott (1949b) found low-purine diets of no therapeutic value in gout. Clinical improvement must be substantial to justify a possibly life-long restriction to a lacto-vegetarian diet with its attendant unpalatability and monotony. The source of endogenous uric acid is believed to be the breakdown of cellular nucleoprotein, especially from the extruded nuclei of normoblasts. Thus, apart from reduction of exogenous sources, the formation of urate can only be decreased at the expense of marrow activity and other vital processes.

The second approach to the therapeutic problem, by the reduction of tubular reabsorption of urate, is based on the following hypothesis. Available evidence suggests that practically all plasma-urate is in filterable form, and that the amount of urate filtered at the glomeruli is the product of filtration rate and plasma-urate concentration (Berliner, Hilton, Yü, and Kennedy, 1950). If we take the following figures as representative of a normal adult person:

$$G = \text{glomerular filtration} = 180 \text{ litres per day};$$

$$P = \text{plasma uric acid} = 4 \text{ mg. per } 100 \text{ ml.};$$

$$U = \text{urine uric acid} = 0.5 \text{ gm. per day};$$

then tubular reabsorption of uric acid =

$$\frac{(P \times G \times 10) - U}{P \times G \times 10} \times 100 = \frac{(4 \times 180 \times 10) - 500}{4 \times 180 \times 10} \times 100 = 93.1 \text{ per cent.}$$

Similar calculations with plasma uric-acid levels of 2 mg. and 10 mg. per 100 ml. give tubular reabsorption figures of 86.1 and 97.2 per cent. respectively. Thus, in a normal human adult, approximately 90 per cent. of urate passing into the glomerular filtrate is reabsorbed by the tubules, and the percentage reabsorbed increases with a rise in plasma uric-acid levels. Berliner, Hilton, Yü, and Kennedy (1950) have demonstrated that if plasma-urate is artificially increased in human subjects a maximum tubular transport capacity occurs at about 15 mg. per minute, and such a reabsorption rate requires a plasma-urate level in excess of 15 mg. per 100 ml., which is rarely exceeded in gout.

The degree of tubular reabsorption of uric acid determines the plasma level, that is the 'renal threshold' for urate. If the rate of tubular reabsorption is decreased, a coincident fall of the plasma-urate level will result, and vice versa. At the commencement of treatment a decrease in tubular reabsorption, for example, from 90 to 86 per cent., is reflected by an increase in the excretion of uric acid in the urine. It is important to realize that once the serum uric acid is stable at its new low level, the urinary excretion will fall and return to a level comparable to that existing before treatment. If the urinary excretion remains high the patient is clearly in a negative uric-acid balance, and it may be tentatively inferred that this excessive excretion is derived from the existing gouty deposits. If the rate of tubular reabsorption could be artificially lowered by means of drugs, it should be possible to maintain a normal serum uric-acid level in gouty persons. Thus the previous calculations show that, with a normal glomerular filtration rate, a reduction of plasma-urate from 10 mg. to 4 mg. per 100 ml. implies a reduction in the tubular reabsorption rate from 97.2 to 93.1 per cent.—a relatively small change of 4.1 per cent.

The above considerations have assumed a normal rate of glomerular filtration. Any alteration in this factor will lead to modifications of the hypothesis. Thus:

$$\begin{aligned} 1(a) \text{ Glomerular filtration} &= 180 \text{ litres per day;} \\ \text{Plasma uric acid} &= 10 \text{ mg. per 100 ml.;} \\ \text{Urine uric acid} &= 0.5 \text{ gm. per day;} \end{aligned}$$

then tubular reabsorption of uric acid =

$$\frac{(10 \times 180 \times 10) - 500}{10 \times 180 \times 10} \times 100 = 97.2 \text{ per cent.}$$

1(b) If plasma uric acid is reduced to 4 mg. per 100 ml., the reabsorption rate becomes 93.1 per cent.

$$\begin{aligned} 2(a) \text{ Glomerular filtration} &= 40 \text{ litres per day;} \\ \text{Plasma uric acid} &= 10 \text{ mg. per 100 ml.;} \\ \text{Urine uric acid} &= 0.5 \text{ gm. per day;} \end{aligned}$$

then tubular reabsorption of uric acid =

$$\frac{(10 \times 40 \times 10) - 500}{10 \times 40 \times 10} \times 100 = 87.5 \text{ per cent.}$$

2(b) If plasma uric acid is reduced to 4 mg. per 100 ml., the reabsorption rate becomes 68.75 per cent.

In 1(a) and 1(b) it will be observed that a normal plasma-urate level may be produced by relatively small changes in the degree of tubular reabsorption, that is by a reduction of 4.1 per cent. To achieve a similar depression in 2(a) and 2(b) the reabsorption rate must be lowered nearly five times as much, that is by 18.75 per cent. Talbott (1943) has observed that, although gouty kidneys do not show any differential inability to clear urate, many gouty persons show evidence of renal impairment with a reduction in glomerular filtration rate. In

such patients, therefore, the maintenance of a lowered plasma-urate level by means of decreased tubular reabsorption will be correspondingly difficult.

It is known that certain drugs have a depressing effect on urate reabsorption. After their initial administration in suitable dosage, the urine uric acid is increased and the plasma uric acid decreased, there being no increase in glomerular filtration (Talbott, 1943). These drugs include salicylates, cinchopen, caronamide, and benemid given orally, and salyrgan, diodrast, glucose, and phenol red given intravenously. The present paper records results of the prolonged use of sodium salicylate.

Pharmacological considerations. Byasson (1877) first showed that sodium salicylate produced an increased excretion of urinary uric acid. Sée (1877) showed a similar effect in gouty patients. This observation was confirmed by Blanchier (1879), and Salomé (1885) pointed out that the salicylate had to be given in large dosage. Dreser (1899) and Rockwood (1909) found that acetyl-salicylic acid had similar effects. Folin and Dennis (1913) introduced a relatively simple colorimetric method for the determination of uric acid in urine and blood. Using this technique Fine and Chace (1914-15, 1915) were able to show that the increased urinary output of uric acid after salicylate administration was accompanied by a fall in blood uric-acid levels. They found that a daily dosage of 6 gm. of sodium salicylate reduced the blood uric-acid level to between one-half and one-third of the initial concentration. Denis (1915) observed similar uric-acid changes, but concluded that the necessary dose of salicylates induced toxic symptoms.

Clinical applications. As long ago as 1876 Kunze reported that salicylates lessened the pain in gout. Cullen (1898) suggested a combination of salicylates with colchicum. Graham (1920) recommended that sodium salicylate be given to gouty people for two or three days of each week or fortnight. He stated that it was useless to give this drug for longer periods, since it caused an increased output of uric acid for two or three days only. Jennings (1937) advised that sodium salicylate should be used in the prophylactic treatment of gout, and he treated his own patients with 80-grain doses daily for three or four days a week. He stated that this régime of intermittent therapy maintained normal levels of uric acid in the blood. Bauer and Klemperer (1944) were unable to confirm Jennings's findings. These authors treated sufferers from gout with 5 to 6 gm. of acetylsalicylic acid on three consecutive days of each week, and found that, although the serum-urate decreased during therapy, it reached high levels on the intervening days. They then tried continuous salicylate therapy, and found a striking reduction in serum-urate concentration at first; but this reduction was temporary, and a return to the original level usually occurred within about three months. They stated that it was impossible to depress the serum uric acid permanently. Among the most recent work in this subject, Gutman (1950) reported that a dosage of salicylate sufficient to reduce the serum uric acid could not be maintained for more than a few consecutive days, because severe salicylism developed. It is the general belief that the progress of gouty changes cannot be arrested, and that chronic symptoms can hardly be allevi-

ated. Bauer and Klemperer (1944) stated bluntly: 'Gout, which is a hereditary disorder, cannot be prevented or cured. Interval treatment with diet, drugs, or a combination of both, as advocated to date has been disappointing. After a careful survey of personal results and a review of the literature, it is concluded that there is no pertinent evidence that these measures alter the clinical course of the disease or even lessen the incidence of attacks.' A review of the published work therefore left the following problems for consideration:

1. If sodium salicylate depresses the serum uric-acid level, for how long can this effect be maintained?
2. Do toxic effects render adequate dosage impracticable?
3. If the serum uric acid can be maintained at a normal level for a prolonged period, is the clinical course of gout affected?

Patients Investigated and Methods

One hundred and fifteen gouty patients have been studied. Thirty-two were labelled as suffering from chronic gout, in that joint pain had persisted for at least three months and was unrelieved by colchicine therapy (Table I). A

TABLE I
Classification of 115 Gouty Patients

Class	Male	Female	Total
Acute	72	11	83
Chronic	28	4	32
All cases	100	15	115

history of one or more attacks of acute arthritis, and a raised serum uric-acid level, were present in all cases. Further diagnostic criteria included some or all of the following: a therapeutic response of acute attacks to colchicine in full dosage (0.5 mg. of crystalline colchicine two-hourly until diarrhoea occurs or pain disappears); presence of urate tophi; and a family history of gout. Therapeutic measures were limited to the following:

1. *Diet.* A high fluid intake was recommended, but no restrictions were imposed as to diet or alcohol.
2. *Colchicine.* Patients were supplied with crystalline colchicine tablets (0.5 mg.) and instructed that at the onset of an acute attack one tablet was to be taken every two hours until the pain was greatly eased or diarrhoea occurred. Continuous colchicine therapy was not prescribed.
3. *Sodium salicylate.* Administration of this drug was limited to cases of chronic gout. It was dispensed in a fluid mixture containing an equal quantity of sodium bicarbonate, a flavouring agent, and sodium sulphite as a preservative. Each dose was made up to half a fluid ounce. The salicylate mixture was usually given three times daily, with the doses spaced equally through the 24 hours. The total daily dosage varied from 60 to 140 grains. The aim was to regulate the salicylate dosage so as to maintain normal serum uric-acid levels and avoid serious toxic symptoms.

Patients were admitted to hospital for the institution of continuous salicylate therapy. After preliminary investigation, including renal function tests, the salicylate was prescribed in an initial dosage of 30 grains thrice daily. Symptoms of salicylism commonly occurred, but unless they were severe patients were encouraged to endure them for a few weeks, and the symptoms usually disappeared. While the patients were in hospital the serum and urinary uric acid were estimated daily. After being sent home the patients maintained continuous salicylate therapy, and attended a gout clinic at intervals of one to four weeks. At each attendance progress was recorded and the serum uric acid was estimated. Occasional measurements were made of prothrombin concentration. Uric-acid determinations were performed by Brown's colorimetric method (1945), and urea estimations by the urease-Nesslerization method (Archer and Robb, 1925); serum-salicylate was estimated by the method of Smith and Talbot (1950), and prothrombin concentration by the method of Quick, Stanley-Brown, and Bancroft (1935).

Results

Effects of purine intake on serum and urinary uric-acid levels. Experiments were carried out with eight men suffering from gout, who received alternate low-purine (lacto-vegetarian) and high-purine diets, each for a period of seven to 11 days. The results are shown in Table II. Facilities did not permit an

TABLE II
Effect of Variation in Purine Intake on Serum and Urinary Uric-Acid Levels in Eight Gouty Patients

Case number	Mean serum uric acid (mg./100 ml.)			Mean urinary uric acid (gm./24 hrs.)			
	Initial	(a) With low-purine diet	(b) With high-purine diet	(b)-(a)	(a) With low-purine diet	(b) With high-purine diet	(b)-(a)
1	5.7(5)*	4.9(7)	6.2(6)	+1.3	0.62(6)	0.82(6)	+0.2
2	6.7(6)	6.5(6)	7.2(6)	+0.7	0.6(6)	0.96(7)	+0.36
3	9.1(6)	8.1(7)	8.0(7)	-0.1	0.69(8)	0.86(8)	+0.17
4	8.2(6)	7.1(11)	7.7(7)	+0.6	0.83(11)	1.06(7)	+0.23
5	6.3(5)	5.2(6)	6.9(3)	+1.7	0.4(6)	0.6(6)	+0.2
6	7.8(5)	5.7(7)	8.2(5)	+2.5	0.7(7)	1.06(6)	+0.36
7	8.5(3)	7.3(10)	8.2(6)	+0.9	0.87(12)	1.0(7)	+0.13
8	8.6(3)	6.2(5)	9.2(4)	+3.0	0.62(4)	0.72(5)	+0.1
Average	7.6	6.4	7.7	1.3	0.67	0.88	+0.21

* Figures in parentheses represent the number of daily estimations performed.

exact control of the purine intake, but the approximate values were 0.2 gm. and 0.5 gm. of purine-nitrogen respectively. The initial figures represent uric-acid readings taken prior to the onset of special diet or therapy. In no case had the patients been taking high-purine foods prior to the experiments. The results show that in only one case did the change from low-purine to high-purine diet fail to produce a rise in the serum uric-acid level. The mean rise for the group was 1.3 mg. per 100 ml. The increase in purine intake caused a rise in the level of urinary uric-acid excretion in all cases, the mean rise for the group being 0.21 gm. per 24 hours.

Serum uric acid in non-gouty persons. The serum uric acid was determined in 100 non-gouty adults, all of whom consumed a normal mixed diet. The mean age among the 50 men was 35.8 years, and among the 50 women 38.7 years. The 100 subjects comprised 27 healthy persons and 73 hospital patients. Patients with renal disease, blood disorders, or pneumonia were not included. Table III shows the frequency distribution of the serum uric-acid levels. The

TABLE III

Frequency Distribution of Serum Uric-Acid Levels in 100 Non-Gouty Adults

Uric acid (mg. per 100 ml.)	Men	Women	Total	
1	2	1	3	
2	1	7	8	
3	13	19	32	
4	17	16	33	
5	11	6	17	
6	6	1	7	
Number of patients	50	50	100	
Uric acid (mg./100 ml.)	Mean Standard deviation	4.54±0.15 1.08	3.82±0.14 1.00	4.18±0.12 1.19

mean serum uric acid among the men was 4.54 ± 0.15 mg., among the women 3.82 ± 0.14 mg., and among the entire 100 persons 4.18 ± 0.12 mg. per 100 ml.

Diurnal variation of serum uric acid and serum-salicylate. In three patients estimations of the serum uric acid and serum-salicylate were made at frequent intervals between consecutive doses of sodium salicylate. All patients had received therapy for several days prior to these tests.

Case 9. Receiving 35 grains of sodium salicylate (with an equal dose of sodium bicarbonate) at 6 a.m., 2 p.m., and 10 p.m.

Time	Serum uric acid (mg. per 100 ml.)	Serum-salicylate (mg. per 100 ml.)
5.55 a.m.	3.7	21
8.00 "	3.1	30
10.00 "	4.1	24
12.00 "	3.5	21
1.5 p.m.	3.8	19
4.00 "	3.3	26
	(range 3.1-4.1)	(range 19-30)

Case 7. Receiving 30 grains of sodium salicylate (with an equal dose of sodium bicarbonate) at 6 a.m. and 6 p.m.

Time	Serum uric acid (mg. per 100 ml.)	Serum-salicylate (mg. per 100 ml.)
10.00 a.m.	3.8	12.6
2.00 p.m.	4.0	9.2
6.00 "	3.1	4.6
	(range 3.1-4.0)	(range 4.6-12.6)

Case 10. Receiving 35 grains of sodium salicylate (with an equal dose of sodium bicarbonate) at 6 a.m., 12 noon, 6 p.m., and 12 midnight.

Time	Serum uric acid (mg. per 100 ml.)	Serum-salicylate (mg. per 100 ml.)
5.55 a.m.	6.3	20.7
6.30 "	5.9	29.5
7.00 "	6.2	31.1
7.30 "	6.0	27.9
8.00 "	6.1	25.8
8.30 "	6.2	25.7
9.00 "	6.0	25.4

(range 5.9-6.3) (range 20.7-31.1)

These tables show little variation in the serum uric-acid levels between consecutive doses of sodium salicylate, irrespective of whether this drug is administered

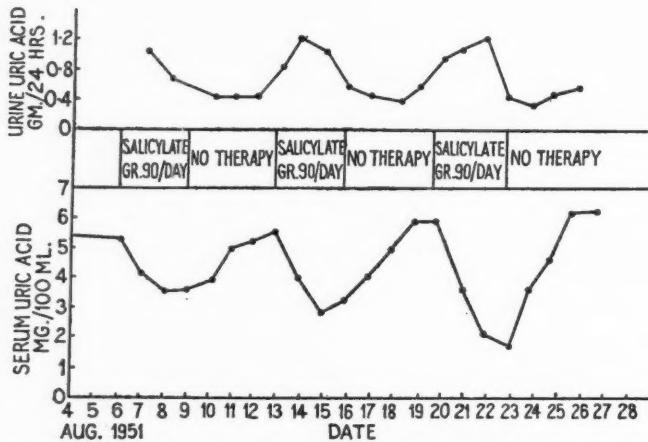


FIG. 1. Serum and urinary uric acid in a gouty patient (Case 11) who was receiving sodium salicylate for three consecutive days of each of three weeks.

six-hourly, eight-hourly or 12-hourly. It may be assumed therefore that, provided the salicylate is administered at regular intervals of not longer than 12 hours, the serum uric-acid level will show little variation.

Intermittent sodium-salicylate therapy. One patient (Case 11) received 30 grains of sodium salicylate (with an equal dose of sodium bicarbonate) thrice daily for the first three days of three consecutive weeks. The patient was in hospital during this time, and received a normal mixed diet except for the exclusion of high-purine foods. Fig. 1 illustrates the uric-acid levels in the serum and urine. It is seen that, although salicylate therapy induced a rapid fall in the serum uric-acid level together with an increase of urinary uric acid, cessation of therapy was followed by an equally rapid return of the uric acid to former levels.

Continuous sodium-salicylate therapy was attempted in 29 patients who had chronic gout. In only one case did the patient refuse to continue with treatment. Fourteen patients received salicylates continuously for more than a year. The daily dosage of salicylate ranged from 60 to 140 grains. The majority of

patients received a constant dosage throughout. In only one patient (Case 12) did it prove impossible to produce an initial lowering of the serum uric-acid

TABLE IV
Serum Uric-Acid Levels and Toxic Symptoms in 14 Patients with Chronic Gout who received Sodium Salicylate Therapy for Periods of at least a Year

Case number	Duration of therapy in months	Mean serum uric acid (mg./100 ml.)		Toxic symptoms after first month of therapy
		Before therapy	During therapy	
13	34	7.8(5)*	4.2(37)	Nil
18	30	6.8(7)	5.4(73)	Occasional tinnitus
19	28	5.0(22)	3.2(73)	Nil
17	27	7.5(8)	2.7(54)	Nil
14	27	4.8(17)	2.2(34)	Occasional slight tinnitus and deafness
7	23	8.5(3)	4.2(33)	Nil
15	21	8.0(18)	3.4(32)	Nil
20	20	7.5(3)	5.1(31)	Occasional deafness
16	19	8.6(14)	3.2(26)	Nil
9	18	10.6(35)	6.1(77)	Bouts of nausea, tinnitus, deafness, and mental confusion
23	18	8.2(17)	3.5(19)	Nil
21	14	7.4(11)	5.0(40)	Bouts of nausea, tinnitus, and deafness
22	13	7.0(10)	4.2(11)	Nil
24	12	5.0(9)	1.8(15)	Mild tinnitus and deafness

* Figures in parentheses represent number of estimations.

level, and this patient was the only one who had severe renal impairment. Table IV shows the serum uric-acid figures before and during salicylate therapy

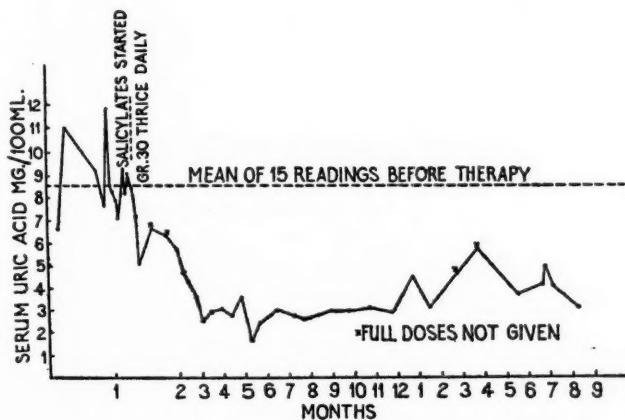


FIG. 2. Case 16. Serum uric-acid levels during 19 months of sodium-salicylate therapy.

in the 14 patients who received it for more than a year. Figs. 2, 3, 4, and 5 illustrate the individual serum uric-acid readings in four cases during salicylate therapy.

Progress during salicylate therapy. 1. *Pain, discomfort, and stiffness of joints.*
All patients experienced marked subjective improvement while receiving sali-

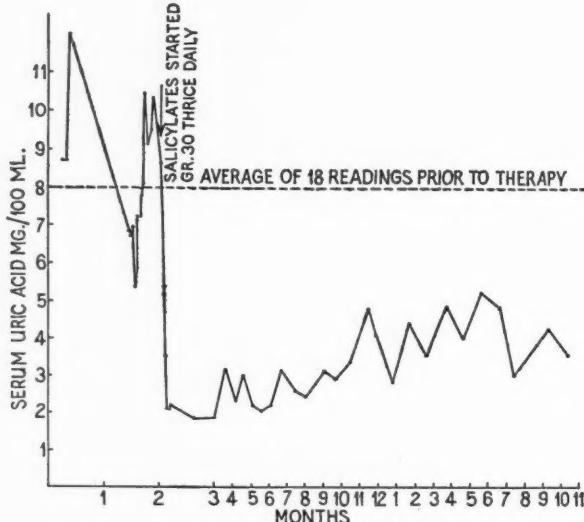


FIG. 3. Case 15. Serum uric-acid levels during 20 months of sodium-salicylate therapy.

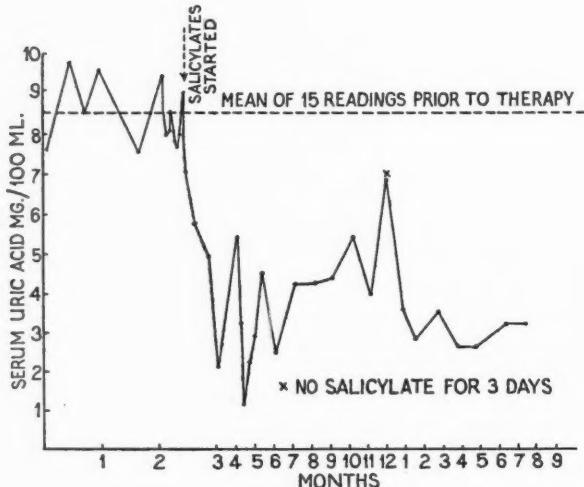


FIG. 4. Case 23. Serum uric-acid levels during 17 months of sodium-salicylate therapy.

cylates. This was so great that 20 of the 28 patients became entirely free from continuous joint symptoms. The time taken to gain relief varied from days to many months, but in all cases the improvement appeared to be both progres-

sive and maintained. The following cases serve to illustrate the type of progress obtained:

Case 13. A man aged 42 years had continuous discomfort in the left ankle for 13 years, causing a permanent limp and rendering long walks and dancing impossible. Therapy started in March 1950. Discomfort disappeared within a

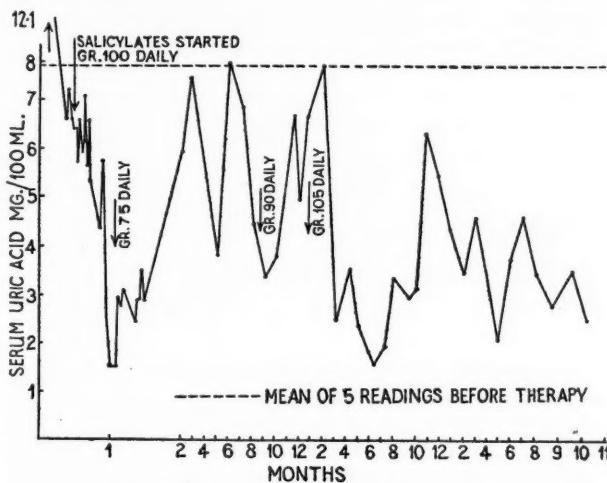


FIG. 5. Case 13. Serum uric-acid levels during 34 months of sodium-salicylate therapy.

few weeks, and since December 1950 the patient has walked normally and danced frequently.

Case 7. A man aged 45 years had not worked for eight years because of continual pains in the joints and inability to stand for longer than five minutes at a time. Therapy started in January 1951. Initial progress was slow, but by the following July he was able to walk two miles for the first time in 10 years. He attended an industrial rehabilitation centre in May 1951 and has worked regularly since. He has remained completely free from continuous pain for the past 18 months, and has only experienced occasional and minor acute attacks.

Case 18. A man aged 51 years was for three years unable to walk more than two miles a day, and for nine months totally incapacitated, with multiple joint pains. Therapy started in May 1950. Pain rapidly lessened, and walking improved, so that after one year he was able to walk up to 12 miles a day. Apart from occasional discomfort in the joints he has remained symptom-free during the past two years.

Case 16. A man aged 49 years had continuous discomfort in the feet and ankles for eight years. Therapy started in May 1951. All discomfort disappeared after two months, and none has recurred during the past 18 months.

2. *Subcutaneous tophi.* No case has been observed in which tophi have enlarged during therapy. In two cases previously conspicuous tophi have disappeared:

Case 22. A man aged 70 years had a 10 years' history of enlarging tophi of the hands and feet, one ulcerating tophus having been excised in March 1951.

Prior to salicylate therapy this patient had conspicuous tophi of various sizes, up to that of a cherry, involving four fingers and the right foot. Therapy started in May 1951. Within two months the tophi were significantly smaller, and after five months they were scarcely detectable.

Case 16. A man aged 49 years had a five-years' history of enlarging tophi of the fingers. Tophi had been removed surgically three years previously, and again in March 1951. Further surgery was contemplated three months later. Prior to therapy the patient had about 15 tophi on his fingers, varying in size up to that of a cherry and interfering with the act of holding a pen. Therapy started in May 1951. Within two months the tophi were appreciably smaller, and after six months all tophi had completely disappeared.

3. Tophaceous ulceration. Four patients had considerable tophaceous ulceration at the start of therapy. In three cases a lowering of the serum uric-acid level was accompanied by healing of the ulcers:

Case 21. A woman aged 61 years had had persistent ulceration of the second left toe, and of one or another finger, for five years. All ulcers healed completely after eight months' therapy, and there has been no recurrence during the past 21 months.

Case 9. A man aged 39 years had had continual ulceration of one or another finger for four years, and was never without a bandaged finger during that time. A large ulcer of the right foot had been present for eight weeks, and had shown no signs of healing. After three months all ulcers had healed, and there was no recurrence during the following 15 months.

Case 25. A man aged 37 years had a large ulcer of the left middle finger of 16 weeks' duration. This ulcer healed completely within three months, and has shown no signs of recurrence during the last eight months.

In the one patient (Case 12) who had serious renal damage, and in whom it proved impossible to lower the serum uric-acid level, no improvement was obtained.

4. Radiological appearances. No deterioration in radiological appearances occurred during salicylate therapy, and improvement was observed in four patients (Cases 9, 16, 17, and 22). This was demonstrated by recalcification which produced a decrease in the size of areas of bone replacement (Marson, 1952).

5. Recurrence of acute attacks. Maintenance of the serum uric acid at normal levels did not necessarily prevent the occurrence of acute gouty attacks. Fig. 6 illustrates the occurrence of such attacks in a patient while he was in hospital under close study. During salicylate therapy, however, the incidence of attacks appeared to diminish, and they were far less severe.

Toxic effects of salicylate. These comprised symptoms of salicylism and hypoprothrombinaemia. A balance had to be struck in each patient between the minimum daily dosage of salicylate required to maintain a satisfactory lowering of the serum uric-acid level and the maximum daily dosage above which toxic symptoms precluded therapy. Sodium salicylate was prescribed in an initial daily dosage of 90 grains. Symptoms of salicylism usually resulted, but unless they were severe the patients were encouraged to persist with the

same dosage for a month, by which time the majority tolerated the drug well. After this initial period only three of the 29 patients under treatment experienced more than occasional and mild symptoms. One patient (Case 21) suffered bouts of nausea, tinnitus, and deafness, and obtained relief by omitting therapy for one or two days; another (Case 9) appeared to acquire an increased sensitivity to salicylate after 18 months of continuous therapy, and was no longer able to

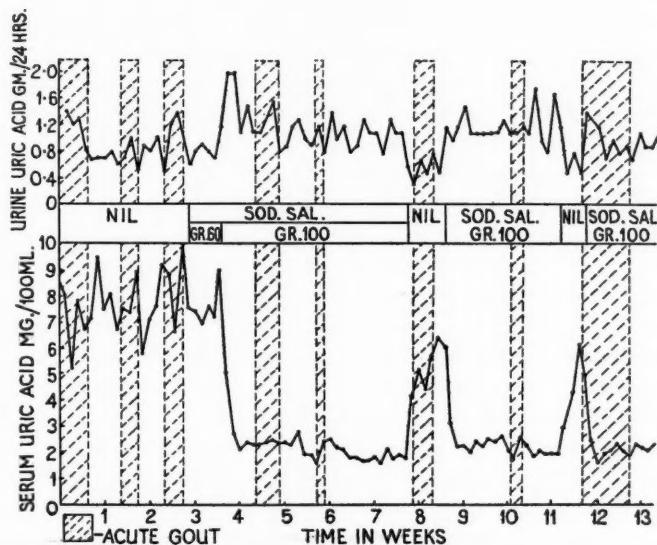


FIG. 6. The influence of sodium-salicylate therapy on the daily serum and urinary uric-acid levels in a gouty patient (Case 7) during a period of three months.

The chart illustrates (1) the wide daily fluctuation of the serum uric-acid level before treatment; (2) the inverse relation between serum and urinary uric-acid levels at the start of treatment. In this patient the increased uric acid excretion persisted after stabilization of the serum uric acid at a low level; (3) a rapid rise in the level of serum uric acid on cessation of sodium-salicylate administration; (4) the occurrence of acute attacks of gout, which were not prevented by considerable lowering of the level of serum uric acid.

continue with the regular medication; another patient (Case 5) suffered an exacerbation of his flatulent dyspepsia, and chose to discontinue therapy after four months. Eleven patients remained entirely free from toxic symptoms after a few weeks of therapy, and, with the exception of Cases 5 and 9, tolerance to salicylate continued to increase in all patients. The plasma prothrombin concentration was estimated at intervals, and showed wide fluctuation in the majority of patients, in spite of a constant salicylate intake. Haemorrhagic manifestations were not observed. Of a total of 200 estimations performed in 16 patients, a fall in prothrombin concentration to below 50 per cent. of normal was seen on 12 occasions, or 6 per cent. of all estimations, and three results (1.5 per cent.) were below 25 per cent. of normal. When the prothrombin

concentration fell below 25 per cent. of normal, oral vitamin K, 10 mg. twice daily, was prescribed until a normal value was obtained.

Discussion

Experiments with alternate high- and low-purine diets have confirmed the general belief that the level of serum uric acid is affected by the purine intake. Such changes were slight, and it appeared unlikely that a purine-free diet could materially alter the clinical course of gout. An attempt was then made to control the serum uric-acid level by the continuous administration of sodium salicylate, and the attempt succeeded in 27 of 29 cases of chronic gout which were studied. The two exceptions comprised one patient with severe renal damage and one defaulter. Bauer and Klemperer (1944) claimed that after three months of medication the control of serum uric acid was lost, and that it returned to previous levels. No such tendency has been observed during the course of the present study, which has covered periods up to 34 months. Apart from the patient who had renal disease, control of the serum uric acid remained satisfactory in all cases throughout the period of observation. The occurrence of an unexpectedly high reading was usually due to neglect by the patients, who occasionally omitted treatment. It was repeatedly emphasized that for success medication had to be continuous, and that the omission of even occasional doses rendered the control of their condition impossible. Gutman (1950) maintained that the frequent occurrence of salicylism made continuous medication impracticable. In the present series toxic symptoms sufficient to prevent continuation of treatment occurred on two occasions only. Many authors (Meyer and Howard, 1943; Butt, Leake, Solley, Griffith, Huntington, and Montgomery, 1945) have referred to lowering of prothrombin levels during salicylate therapy. Our observations confirm these findings, and the levels were shown to vary widely. In no case has haemorrhage resulted, and low prothrombin concentrations were satisfactorily restored by oral vitamin K. Considerable improvement occurred in all patients during the periods in which sodium salicylate maintained the serum uric acid at normal or nearly normal levels. Pain and stiffness of the joints disappeared in 20 of 28 patients. Several, previously crippled, were restored to normal activity for the first time in many years. Tophi were noticed to disappear, ulcers to heal, joint destruction to be arrested, and the range of movements to be increased. The most striking proof that urate deposits were absorbed under this treatment was provided by radiological study (Marson, 1952) in four cases. These radiographs demonstrate recalcification and restoration of bone structure. It is pertinent to inquire for how long this strict regimen should be imposed. Cessation of salicylate therapy in a few cases has not resulted in an immediate return of symptoms, but the serum-urate level rises rapidly. The extent of such symptomatic remissions is as yet unknown, and it may be possible to maintain adequate control of the disease by the administration of salicylates for a long period of each year. Further studies intended to clarify this point are in progress. It may again be emphasized that continuous treatment by salicylate will not entirely prevent the occurrence of

attacks of acute gout, but there is little doubt that such attacks are reduced in frequency and severity. This aspect of the disease presents little difficulty, as the colchicine treatment of acute attacks is highly satisfactory.

The pharmacological action of sodium salicylate has been shown to depend on the capacity of this drug to block tubular reabsorption of uric acid. Other drugs with a similar action on the tubules might be expected to produce comparable results. Our experience has shown acetylsalicylic acid to be less effective, and salicylamide to be without action. I have been unable to find reports of the continuous administration of cinchophen, and in view of its potential hepatotoxic effects this form of treatment was regarded as unjustified. Recently Gutman and Yü (1950) have reported on the use of caronamide. They obtained satisfactory depression of serum uric-acid levels with a dosage of 12 to 13.5 gm. daily; but the large number of tablets and various toxic reactions rendered this treatment objectionable. The same authors later tried benemid, a drug structurally related to caronamide, in a daily dosage of 2 gm. Toxic reactions were less, but it appeared to provoke acute gout in some patients. We have used benemid in five patients, but in two of these serious sensitivity reactions occurred on the tenth day of therapy. Our present impression is that continuous sodium-salicylate therapy constitutes the most practicable method of controlling the levels of serum uric acid in cases of chronic gout.

Acknowledgements

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Summary

1. The importance of treatment designed to lower the serum uric-acid levels in patients with chronic gout is stressed. The principles of such treatment are discussed, and the literature reviewed with special reference to sodium salicylate.
2. Sodium salicylate was used in the treatment of 29 patients with chronic gout, to whom it was administered continuously for periods of up to 34 months.
3. It is shown that sodium salicylate can be tolerated for prolonged periods in a dosage sufficient to maintain the serum uric acid at normal or nearly normal levels. Tolerance to the drug usually develops within a few weeks. With reasonable control there is little risk of haemorrhagic complications.
4. Effective control of the serum uric-acid level produces marked alleviation of the symptoms of chronic gout, and the arrest and partial repair of the destruc-

tive changes induced by urate deposition. Of the 29 patients studied, 20 obtained entire relief from pains in the joints. The treatment is ineffective when there is severe renal damage.

5. Sodium salicylate, given in a daily dosage of 90 grains for three consecutive days of each week, failed to maintain continuously a lowered serum uric-acid level.

6. Experiments with diets of varying purine-content confirmed the belief that the serum uric acid cannot be effectively controlled by the limitation of purine intake. There is probably no justification for dietetic restriction.

7. Colchicine rarely fails to relieve the symptoms of acute gout.

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PROGNOSIS IN ACUTE DISSEMINATED ENCEPHALO-MYELITIS; WITH A NOTE ON NEUROMYELITIS OPTICA¹

By HENRY G. MILLER AND MICHAEL J. EVANS

(From the Royal Victoria Infirmary, Newcastle upon Tyne)

THE present paper is based on a follow-up study of 27 patients who recovered from illnesses diagnosed as acute encephalomyelitis in Newcastle upon Tyne between 1932 and 1942. It does not deal with the clinical or pathological minutiae of the disease; its aims are to clarify the natural history of acute disseminated encephalomyelitis and to examine the relationship between this condition and other demyelinating diseases, disseminated sclerosis and neuromyelitis optica in particular. For present purposes acute disseminated encephalomyelitis may be defined as an acute or subacute inflammatory non-suppurative disease of the nervous system, characterized by disseminated or focal clinical signs, encountered in its typical forms after Jennerian vaccination or in association with measles, but occurring similarly after banal infections and also in the absence of recognizable preceding illness. The reasons which have led to the grouping together of patients with such illnesses under the label of 'acute disseminated encephalomyelitis' will be critically examined in the discussion.

Cases of acute disseminated encephalomyelitis, particularly when they follow exanthemata, are often loosely referred to as examples of 'virus encephalitis'. They are, however, pathologically distinct from all those forms of predominantly polioclastic encephalitis which have been proved to be due to virus infection. Clinical differentiation between acute disseminated encephalomyelitis and encephalitis of virus origin is not always easy, especially when the former disease arises spontaneously, in the absence of a preceding exanthem or some other clearly recognizable respiratory or general infection. Acute epidemic encephalitis lethargica is at present a great rarity, and differentiation should be possible because of the absence of meningism, the infrequency of myelitic, radicular, or neuritic syndromes, and the prominence of pupillary changes, ophthalmoplegia, and extrapyramidal signs. Although the encephalomyelitis which occasionally complicates herpes zoster is probably a direct result of invasion by the causative virus, it may present a picture clinically indistinguishable from acute disseminated encephalomyelitis, in which case diagnosis must depend on the presence of the characteristic eruption. An appreciable lymphocytic pleocytosis in the spinal fluid is an almost invariable finding in a virus meningo-encephalitis, such as mumps or lymphocytic choriomeningitis, which

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is a predominantly meningitic illness with little clinical evidence of frank encephalitis. Outside the British Isles the difficulties are more real. In the arthropod-borne virus encephalitides of Japanese B, St. Louis, and equine types, pleocytosis is the rule. In the two former instances focal neurological symptoms are rare, but equine encephalomyelitis, particularly in its Eastern form, may present a picture closely similar to that of acute disseminated encephalomyelitis.

In view of their clinical and pathological similarities, the relationship between acute disseminated encephalomyelitis and disseminated sclerosis is a problem of perennial interest, and it is of more than academic importance in its bearing on the advice as to prognosis which is given to patients recovering from the acute illness and to their families, with regard particularly to the possible subsequent development of progressive organic nervous disease. Most physicians give a good prognosis in cases of acute encephalomyelitis, but the evidence on which such statements are based is fragmentary, and they are often made with a mental reservation that some such illnesses, otherwise characteristic, may represent initial episodes of disseminated sclerosis, with all the prognostic implications of the chronic disease. McAlpine (1931) and Stout and Karnosh (1933) followed up four and 28 cases respectively of 'spontaneous' acute disseminated encephalomyelitis for a few years after their acute illnesses, and although a number of their patients showed some residual disability, and one patient in the second series relapsed, there was no other example of the development of further neurological symptoms during a relatively short period of observation. In 1946, however, McAlpine reported that two of his four patients, and a further patient seen in 1931, had developed relapsing neurological symptoms, with one fatality. Their symptoms were not unequivocally those of disseminated sclerosis, and McAlpine considered that these observations did not necessarily invalidate the original diagnosis. Thygesen (1949) followed up 29 patients in whom a firm diagnosis of acute disseminated encephalomyelitis had been made eight to 15 years previously. Four patients had died, seven had developed disseminated sclerosis, and four had proved to be cases of encephalitis lethargica. Fourteen patients were well, and had had no further neurological incidents. Of 31 further patients in his series in whom the initial diagnosis of acute disseminated encephalomyelitis had been considered more doubtful, 19 subsequently developed disseminated sclerosis, three encephalitis lethargica, and two evidence of cerebro-vascular disease; in the remaining seven the original diagnosis appeared to be confirmed by the absence of sequelae. Van Bogaert (1950) followed up 19 cases similarly diagnosed between 1927 and 1932. One of these patients had died in the acute illness, four had developed disseminated sclerosis and one a very similar illness, while 11 patients were well.

Patients Investigated

The present paper is based chiefly on a follow-up study of the survivors among 29 patients consecutively diagnosed as suffering from acute encephalomyelitis and admitted to the Royal Victoria Infirmary between 1932 and 1942.

All these patients manifested acute disseminated or focal inflammatory non-suppurative disease of the neuraxis, without any relevant previous history of neurological symptoms or any clinical or serological evidence of syphilis. Cases are excluded in which the diagnosis was clearly questionable, or in which an initial diagnosis of encephalomyelitis was disproved by further clinical observation of the acute illness or by autopsy. The latter group comprised patients subsequently shown to be suffering from bulbar poliomyelitis, polyneuritis of pregnancy, uraemia, hypertensive encephalopathy, and recurrent bleeding from intracranial aneurysm. In three patients with acute myelitic syndromes a diagnosis of 'acute myelitis, probably disseminated sclerosis' was made on the basis of some neurological incident in the past history, or of some associated neurological finding. In these three patients, also excluded from the present series, subsequent observation showed the clinical suspicion of disseminated sclerosis to have been correct. The unqualified diagnosis of 'encephalitis' is frequently a gesture of despair, and when such a label was applied to cases of coma without focal signs in the central nervous system, such patients—a number of whom recovered—were also excluded, although no doubt some of them may have suffered from acute encephalomyelitis. Of the 29 patients admitted to hospital with encephalomyelitis during the period under consideration seven died, and in six of these the diagnosis was confirmed by autopsy. All the remaining 22 patients were traced. Five had subsequently died. In 1952 14 survivors were personally re-examined, and the remaining three were examined on our behalf by physicians elsewhere in the British Isles. For various reasons a series of cases of encephalomyelitic illness collected from the records of a general hospital tends to be not entirely representative. Many patients in whom the disease is post-exanthematous remain in, or are admitted to, hospitals for infectious diseases. Of those in whom it is 'spontaneous' an appreciable number with encephalitic symptoms are similarly admitted as suspected cases of meningitis. The teaching hospital tends to collect proportionately more myelitic cases, in which the nature of the illness is initially less apparent. In an attempt to compensate this bias, and to augment the series, we have followed up also four patients with 'spontaneous' encephalomyelitic syndromes who were admitted during the same period to the City Hospital for Infectious Disease, Newcastle, and one private patient, making a total of 27 cases of acute disseminated encephalomyelitis followed for between one and two decades after the acute illness. Of these cases only three were associated with exanthemata; several of the patients gave a history of an immediately preceding non-specific illness, usually an upper respiratory tract infection. Of the total of 34 patients discussed 16 were male and 18 female. Their ages were distributed among the first five decades of life, ranging from two and a half to 49 years. Of 20 cases with encephalitic symptoms six were fatal; of 10 patients with purely myelitic illnesses only one died during the acute illness.

Fatal Cases

Before the consideration of patients who recovered, which is the main purpose of the present paper, the seven fatalities among the hospital series of 29

patients merit brief presentation. The majority of patients who suffer from acute disseminated encephalomyelitis recover, often dramatically and often with slight residual disability; a consideration of fatal cases might be expected to yield some clues as to individual prognosis. The duration of the illness in the seven patients who succumbed was 4, 5, 19, 26, 57, 140, and 270 days respectively.

TABLE I
Fatal Cases

<i>Case number</i>	<i>Age (years)</i>	<i>Sex</i>	<i>Aetiological factors</i>	<i>Clinical features</i>	<i>Cerebro-spinal fluid</i>	<i>Duration of illness (days)</i>
1	40	M	0	Fever, headache, hiccup, and delirium. After 24 hours coma with right extensor plantar response	12 cells per c.m.m.	5
2	25	F	Dental extraction	Stupor followed by coma. Nystagmus. Flaccid tetraplegia. No fever	Normal	4
3	16	F	0	Gradual progression of malaise, drowsiness, and coma. Right hemiparesis. Bilateral extensor plantar responses	Normal	26
4	2½	M	'Feverish cold'	Gradual personality - deterioration with loss of speech and incontinence. After 6 months, spastic paraplegia. Later high fever, myoclonus, generalized convulsions, coma	Normal	270
5	29	F	0	Sudden paraplegia, with improvement. Relapse after 10 days with delirium, stupor, and coma; neck stiffness, right hemiparesis, bilateral extensor plantar responses	Normal	19
6	38	M	0	Gradual development in 5 months of spastic tetraplegia. Terminal acute illness: tetraplegia, nystagmus, neck stiffness, delirium, and coma	Normal	140
7	17	M	Preceding subacute respiratory illness	Root pains, progressive paraplegia, retention of urine, sensory loss below T 8. Death from streptococcal pyelonephritis	Normal	57

tively. The first two fatalities occurred in patients who rapidly became comatose and died without regaining consciousness:

Case 1. A 40-year-old man was admitted to hospital in April 1937 with high fever, intense vertical headache, slight cough, mental confusion, and persistent hiccup. Within 24 hours of the onset delirium gave place to coma, and the right plantar response became extensor. The spinal fluid showed a moderate increase in protein and lymphocytes, and the patient died in five days without regaining consciousness.

Case 2. A woman of 25 years was admitted to hospital in March 1938. The day before admission she had several teeth removed under local anaesthesia because of pyorrhoea, and the next morning she could not be roused. On examination she had a severe flaccid tetraplegia, more marked on the right, with bilateral extensor plantar responses, gross spontaneous nystagmus, but no fever, meningism, or change in the spinal fluid. She died four days after the onset of the illness, her stupor having given place to profound coma and complete flaccid paralysis with disappearance of the deep reflexes.

The second of these cases is of some interest in that it followed dental extraction: a similar example was reported by van Bogaert (1950). The most

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fulminating cases of acute disseminated encephalomyelitis frequently yield a history of the patient retiring to bed apparently well, and being found comatose or dead in bed the next morning. Such a history is not uncommon in cases of post-vaccinal encephalomyelitis. In other cases a somewhat similar illness was of longer duration and more subacute development:

Case 3. A 16-year-old girl was admitted to hospital in January 1935. She had been 'off colour' for 10 days, drowsy for five days, and comatose for three days. On examination she showed unequal, sluggish pupils, a right hemiparesis, and bilateral extensor plantar responses. The spinal fluid was normal. Her coma deepened, and she died after an illness of 26 days' duration.

Case 4. A boy of two and a half years was admitted to hospital in April 1942. Six months before admission he had had a feverish cold. Since that time he had gradually become unable to walk, and had developed difficulty in feeding himself, progressive loss of speech and interest, and more recently incontinence. Examination revealed spastic paraplegia without sensory loss, and clumsiness of the hands. His general behaviour was that of a child of twelve months. During his stay in hospital he developed high fever, screaming attacks, muscular twitching, and ultimately generalized convulsions and deep coma. The spinal fluid remained normal, and death occurred nine months from the onset of the illness.

In two patients a myelitic syndrome was followed, after intervals of 14 days and 20 weeks respectively, by a fatal encephalitic relapse:

Case 5. A woman of 29 years was admitted to hospital in March 1936. Fourteen days before admission she developed sudden stiffness and uselessness of both legs while standing at a table, and had to be helped to bed. During subsequent days the condition improved, and she was able to walk round the room. Ten days later the condition relapsed, with pronounced weakness more marked in the right leg, and the rapid onset of delirium. On admission she was stuporose and irritable, with neck stiffness, a marked right hemiplegia, symmetrical absence of the abdominal reflexes, and bilateral extensor plantar responses. The spinal fluid remained normal, and the patient died in coma 19 days after the onset of the illness.

Case 6. A 38-year-old man was admitted to hospital in May 1936. Five months previously he had developed numbness in the fingers of the left hand, which spread up the arm to the trunk and then involved the left leg. Within a month the opposite side of the body was similarly affected, and three months before admission examination showed evidence of a spastic tetraplegia of moderate degree, without sensory change. During the week preceding admission he developed severe pains in the limbs, and became mentally confused. Examination revealed severe spastic tetraplegia, with gross nystagmus and neck stiffness. The spinal fluid was normal. Mental confusion gave place to coma, and he died seven days later after an illness of 20 weeks' duration.

In all the above cases profound coma preceded death, but in one patient a purely myelitic syndrome proved fatal within eight weeks because of pyelonephritis:

Case 7. A boy of 17 years suffered for several months from a recurrent and apparently non-specific chest infection, characterized by febrile episodes and

a variable and recurring mid-zonal opacity in the left lung. This illness resolved, clinically and radiologically, six weeks before his admission to hospital in June 1934. Twelve days before admission he was seized by acute girdle pains, progressive weakness in the legs, and retention of urine with dribbling. There was no meningism, and no evidence of encephalitis. Examination showed a severe transverse cord lesion at T8, with high fever, normal spinal fluid, and a resistant streptococcal pyuria. He remained in hospital for six weeks, and was finally discharged unimproved at the insistence of his parents, still febrile and still with infected urine; he died three days later, almost certainly as the result of an ascending pyelonephritic infection.

In Cases 1 to 6 the condition was confirmed by autopsy. In general the changes seen were similar to those first clearly described by Brain, Hunter, and Turnbull in 1929. These authors classified the pathological appearances under three headings: (1) cases showing cerebral oedema, with or without acute neuronal degeneration; (2) haemorrhagic encephalitis; (3) established changes comprising perivascular infiltration and demyelination. Subsequent pathological observations have lent further support to the view that such changes may represent phases of varying acuteness and severity in the development of a single pathological process. In Case 2 oedema, with occasional ring haemorrhages, was the only abnormality. In Case 1 the encephalitis was frankly haemorrhagic. In Case 6 a chronic myelitis, most severe in the cervical region, was associated with the finding of an acute perivenous encephalitis of more recent development. Comparison of fatal cases with cases of recovery indicate that changes in the spinal fluid are of little value in prognosis. The only fatal case showing such changes was one of the most acute examples (Case 1), but the other equally fulminating case (Case 2) yielded a normal fluid. Pleocytosis and increased protein-content are probably somewhat more common in long-standing cases with clinical evidence of widespread pathological involvement of the neuraxis, but even in illnesses of this type (Case 6) the fluid may remain unaltered. The only clinical feature which can be clearly correlated with prognosis is the depth of disturbance of consciousness. Except Case 7 (and death from urinary infection would be appreciably less likely today) every fatal case manifested deep coma as the outstanding clinical feature of a predominantly encephalitic illness. Purely myelitic lesions threaten life only by way of respiratory failure, pressure sores, or urinary infection, and fatal cases occur almost entirely among patients with encephalitic illnesses who become comatose.

Cases of Recovery

The 27 patients who recovered comprised 14 cases of encephalomyelitic illness, 10 instances of transverse myelitis, and three cases classified in the hospital records as encephalomyelitis, in which loss of vision was the most prominent feature. Re-examination 10 to 20 years after the acute illness revealed evidence of subsequent episodes of neurological illness in two cases of encephalomyelitis (Cases 20 and 21), three of transverse myelitis (Cases 29, 30, 31), and one of the cases showing visual failure (Case 34).

Encephalomyelitis

Of the 14 patients who had encephalomyelitis and recovered, three showed complete disappearance of symptoms and signs and no recurrence during periods of 10, 12, and 17 years respectively.

Case 8. Encephalitis following 'influenzal' illness, with complete recovery in two weeks and no further episodes during the subsequent 10 years.

This 26-year-old woman was admitted to hospital in January 1942. Three weeks previously she had had an influenzal illness, which began with a rigor

TABLE II
Complete Recovery Without Recurrence

Case number	Age (years)	Sex	Aetiological factors	Clinical Features	Cerebro-spinal fluid	Duration of illness (days)	Follow-up (years)
8	26	F	'Influenza' and bronchitis 10 days before	Headache and vomiting followed by delirium and stupor. Neck stiffness, strabismus, and incontinence. Absent abdominal, depressed deep reflexes. Headaches persisted for 6 months	36 cells per c.mm.	17	10
9	7	M	Varicella	Headache, vomiting, stupor. Flaccid paraplegia, right extensor response. Varicella rash 72 hours later. Ataxia evident on recovery of consciousness	Normal	36	12
10	6	F	0	Gradual weakness of legs with ataxia. Nystagmus; increased deep reflexes; plantar reflexes equivocal. Drowsiness for 4 days followed by transient hemiparesis	Normal	28	17

and developed into an acute bronchitis with high fever. Ten days before admission, when her respiratory symptoms were clearing up, she developed an intense headache and vomited repeatedly. Three days before admission she became mentally confused and stuporous. On examination she could not be roused, but was restless, with slight fever, marked neck stiffness, strabismus, and double incontinence. The abdominal reflexes were absent, the deep reflexes depressed, and plantar responses flexor. The spinal fluid contained 36 lymphocytes per c.mm. Improvement after admission was rapid, and seven days later she was rational, but had complete amnesia as to the preceding 10 days. Double vision persisted for a further week, but on discharge from hospital 16 days after admission she was well except for headaches. Intermittent headaches persisted for six months, and then cleared up completely. Re-examination in 1952 showed no abnormal findings, and there had been no neurological incidents in the subsequent 10 years.

Case 9. Acute encephalomyelitis with drowsiness, spasticity, and ataxia, developing concurrently with varicella. Complete recovery without sequelae during the subsequent 12 years.

This seven-year-old boy was admitted to hospital in July 1940. Fourteen days after exposure to a case of chickenpox he developed headache and pains in the legs, from which he recovered in three days. Four days later a similar episode occurred, on recovery from which (25 days after exposure to the exanthem) he awoke with headache, drowsiness, and pronounced weakness of the legs. Vomiting became profuse, and within 72 hours a mild varicella rash appeared both in the patient and in his similarly exposed sibs. Examination in hospital revealed the characteristic eruption, drowsiness, vomiting, and

flaccid weakness of the legs with a right extensor plantar response, but without sensory change or sphincter disturbance. The spinal fluid was normal. Recovery began eight days later with the disappearance of drowsiness, and within 14 days from this time he was able to walk with assistance, though he remained profoundly ataxic for a further two weeks. A week later, however, he was free from disability and abnormal physical signs. On re-examination

TABLE III
Complete Symptomatic Recovery with Residual Signs

Case number	Age (years)	Sex	Aetiological factors	Clinical features	Cerebro-spinal fluid	Time unable to work (days)	Follow-up (years)	Residual signs
11	26	F	Rubella 14 days before	Headache, vomiting, and fever, followed after a week by right facial palsy and left hemiplegia with equivocal right plantar response	Normal	21	11	Diminished left abdominal reflexes, exaggerated knee- and ankle-jerks, equivocal plantar responses
12	18	M	0	Sudden fever, headache, vomiting, meningismus, and delirium. Depressed reflexes and equivocal plantar responses. Rapid recovery	Normal	36	14	Increased reflexes in left arm and both legs
13	20	M		Fever, headache, delirium. Progressive spastic tetraparesis with muscular wasting and tenderness. Extensor plantar responses	Normal	330	16	Increased knee- and ankle-jerks and extensor plantar reflexes. No wasting. No spasticity
14	17	M	Chilling 1 day before	Acute paraparesis with headache, drowsiness, and retention of urine. Absent deep reflexes, extensor plantar responses. Sensory loss below T 10	Normal	120	18	Absent cremasteric reflexes. Diminished lower abdominal reflexes

in 1952 there was no history of subsequent illness of any significance, and examination was entirely negative.

Case 10. Acute neurological illness, with pyramidal and cerebellar signs and drowsiness, at the age of six years, clearing up rapidly. No recurrence in the subsequent 17 years.

Two weeks before admission to hospital in April 1935, this previously healthy six-year-old girl complained of pain in the legs, and fell backwards on walking. Five days after the onset she became grossly ataxic, and was quite unable to stand. On examination she had gross nystagmus on lateral deviation, generalized increase of deep reflexes, and equivocal plantar responses, with retention of the abdominal reflexes. This condition persisted for four days, during which time she was drowsy. Improvement was rapid. Seven days after admission she showed only nystagmus and a slight right hemiparesis. Four weeks after her admission to hospital all symptoms and signs had disappeared, and she was able to walk perfectly. On re-examination in 1952 she was in perfect health. She had had no subsequent neurological symptoms, was delivered of a healthy baby in 1951, and showed no abnormal signs on neurological examination.

Four patients showed complete or almost complete recovery of function, with some residual physical signs, maintained without neurological incident for periods of 11, 14, 16, and 18 years respectively.

Case 11. Mild encephalomyelitis, with headache, facial palsy, and spinal cord signs, following rubella. The condition cleared rapidly, leaving minor residual signs but no disability 11 years later.

This 26-year-old woman was admitted to hospital in June 1941 with a sudden attack of headache and vomiting 14 days after recovery from a moderately severe attack of rubella. She was febrile, there were no physical signs in the nervous system, the spinal fluid was normal, and the headache and vomiting disappeared within 48 hours. She was sent home, but during the subsequent seven days she had repeated moderately severe frontal headaches. At the end of this period she developed a right facial palsy of lower motor-neurone type, and four days later weakness and stiffness of the left leg. On readmission to hospital examination revealed typical Bell's palsy on the right, increased reflexes in the right arm without relevant symptoms or signs, absent abdominal reflexes on the left, and increased knee- and ankle-jerks, with an extensor plantar response on the left and an equivocal response on the right. She improved rapidly, and 10 days later the only residual sign was some facial weakness. There were no subsequent neurological incidents, and re-examination in 1952 revealed no abnormal signs except that the abdominal reflexes tired much more easily on the left than the right, both knee- and ankle-jerks were abnormally brisk, and both plantar responses were equivocal.

Case 12. Acute encephalomyelitis with complete recovery of function, but minor residual signs still present 14 years later.

An 18-year-old boy was admitted to hospital in 1938 with an illness of sudden onset presenting high fever, headache, vomiting, and difficulty in micturition. He was confused and violent, with meningism, marked depression of all deep reflexes, and equivocal plantar responses. There was no history of preceding illness, and the spinal fluid was normal. He recovered rapidly, discharged himself from hospital six days after admission, and returned to work a month later. On re-examination in 1952 he was free from symptoms, and had had no subsequent neurological complaints. Examination revealed pronounced increase of reflexes in both legs and in the left arm, without disability, and with retention of the abdominal reflexes and normal plantar responses.

Case 13. Febrile encephalomyelic illness with spastic tetraplegia and signs of an associated polyradiculitis. Signs of spastic paraparesis present 16 years later without disability.

This 20-year-old man was admitted to hospital in 1936 with a febrile illness of sudden onset characterized by intense headache and pain across the shoulders, mental confusion, and rapidly progressive muscular weakness greatest in the lower limbs. Examination revealed a symmetrical spastic tetraplegia more marked in the lower limbs, with generalized wasting and tenderness of muscles, most severe in the proximal segments. The deep reflexes were generally increased, with extensor plantar responses. The abdominal reflexes were retained. There was no sensory impairment, sphincter disturbance, or change in the spinal fluid. Fever and headache disappeared during the course of seven days, and simultaneously the mental state cleared, leaving a period of amnesia. Progressive improvement ensued, and the patient returned to work in 11 months. Re-examination in 1952 revealed increased knee- and ankle-jerks and extensor plantar responses, without spasticity, weakness, or wasting.

Case 14. Transverse myelitis with minimal encephalitic signs, following chilling. Rapid and almost complete recovery, with no recurrence of nervous symptoms during the subsequent 18 years.

This 17-year-old miner was admitted to hospital in August 1934. Three days before admission he had worked all day submerged to the waist in cold water. The following morning he had generalized muscular pains, and the day before

TABLE IV
Non-Progressive Residual Disability; Death during follow-up period

Case number	Age (years)	Sex	Aetiological factors	Clinical features of acute illness	Cerebro-spinal fluid	Subsequent history
15	26	F	?Pyelitis	Headaches, drowsiness, and right hemiplegia. Aphasia. Meningism. Equivoocal pyramidal signs on left	100 cells per c.mm.	Speech recovered after 2 months. Able to walk after 6 months. Death from pyelonephritis 1 year after onset
16	49	F	0	Headache and delirium for 3 weeks. Early papilloedema, right abducens palsy, absent knee- and ankle-jerks, flexor plantar responses	56 cells per c.mm.	Recovery after 18 days. Great emotional lability, without intellectual deterioration, persisted until death from cardiac infarction 6 years later
17	44	M	0	Headache, vomiting, and neck stiffness, followed by sudden paraplegia. Disorientation, nystagmus, spasticity of left arm and both legs. Extensor plantar responses	Normal	Able to walk after 6 weeks. Residual stiffness and weakness of legs. Death from carcinoma of pancreas 7 years later

admission he fell to the ground with a sudden onset of weakness and loss of sensation in the legs. Within four hours he became very drowsy, complained of intense occipital headache, and developed retention of urine. On examination he could be roused with difficulty, and was slightly febrile, but there was no meningism. There were signs of a transverse lesion at T 10, with absence of the deep reflexes, extensor plantar responses, profound loss of superficial sensation, and impairment of vibration sense below the level of the lesion. The abdominal reflexes were absent; the spinal fluid was completely normal. Drowsiness and headache disappeared within three days, and improvement in the limbs began three weeks later. Six weeks after the onset the patient was able to walk, and he returned to work two months later. He subsequently served for six years in the Army, and was able to march for 30 miles, his only complaint being some aching in the left leg on walking long distances in cold weather. On re-examination in 1952 there were no abnormal signs except absent cremasteric reflexes and a tendency for the lower abdominal reflexes to tire easily.

Seven of the 14 encephalomyelic patients showed appreciable subsequent disability. In Cases 15, 16, and 17 this disability was clearly a non-progressive residuum of the acute disease. In Case 16 it was emotional, and not associated with abnormal physical findings. Two of these three patients were in the older age-group (aged 44 and 49 years); it is remarkable that all three died from illnesses apparently unrelated to the cerebral syndrome, after intervals of one, six, and seven years, without recurrence of neurological symptoms. In view of subsequent developments it is clearly possible that the initial diagnosis of encephalomyelitis in Cases 15 and 16 was erroneous, and that these were in

fact instances of cerebrovascular accident. In Case 17, however, it is difficult to postulate any connexion between the cerebral illness and the cause of death.

Case 15. Probable acute encephalomyelitis with hemiplegia. Partial recovery, with severe residual disability, and death 12 months later from pyelonephritis.

This 26-year-old woman, who had a past history of recurrent pyelitis without hypertension or nitrogen retention, complained of headaches and drowsiness for three days, followed by gradual loss of use of the right arm and leg. On examination one week later she was confused and drowsy, with meningism and fever, right hemiplegia and aphasia, symmetrical absence of the abdominal reflexes, and a right extensor and an equivocal left plantar response. Her spinal fluid repeatedly showed a lymphocytic pleocytosis varying between 100 and 60 cells per c.mm. The fever and drowsiness cleared up within a week, speech returned eight weeks later, and six months after the onset she was able to walk with a hemiplegic gait. Ten months after the onset of the cerebral illness she developed an uncontrollable pyelonephritis, from which she died within a few weeks.

Case 16. Acute encephalomyelic illness with lymphocytic pleocytosis. Recovery except for persisting emotional lability. Death from coronary occlusion six years later.

This 49-year-old woman was admitted to hospital in 1935 with a three weeks' story of intense vertical headache and mental confusion. On admission she was irritable and disorientated. Examination revealed early bilateral papilloedema, a right sixth-nerve palsy, and absent knee- and ankle-jerks, with flexor plantar responses. There was mild meningism, and the spinal fluid was under increased pressure and contained 56 lymphocytes per c.mm. The blood-pressure was normal, and there was no evidence of significant arteriopathy. After 18 days she had improved greatly, and subsequently she remained well except that she was very much more uninhibited emotionally than before, and was prone to laugh or cry immoderately on slight provocation. There was no evident impairment of memory, and she was able to lead a normal life until her death from coronary occlusion six years later.

Case 17. Acute encephalomyelitis with disorientation, cerebellar symptoms, and signs of a pyramidal-tract lesion affecting one arm and both legs. The illness left mild residual disability, showing slight improvement during the subsequent seven years; the patient then died of cancer.

This 44-year-old man was admitted to hospital in 1941 after three days of headache, vomiting, and neck stiffness, and the more recent development of sudden profound weakness of both legs. He was disorientated, with gross nystagmus on looking to the left, and ataxic spasticity of the left arm and both legs. The abdominal reflexes were retained, and the plantar responses extensor; there was no sensory change. He had meningism and a temperature of 102° F., but the spinal fluid was normal. Five days later he was mentally clear, and a fortnight later improvement began in the left arm, and to a less extent in both legs. Six weeks after the onset he was able to walk with a spastic and slightly ataxic gait. His residual disability was stiffness and weakness of both legs, necessitating an occasional few days' rest from work; the legs sometimes let him down. During the subsequent seven years his disability improved slightly. He died in 1948 from cancer of the pancreas. Neurological examination on admission to hospital at that time had revealed mild spasticity of the legs, with equivocal plantar responses, as the only abnormal finding.

In the remaining four cases of encephalomyelic illness which showed residual disability, the nature of the subsequent condition is open to doubt, and is dealt with more fully in the discussion. In two of these patients (Cases 18 and 19) the disability was apparently non-progressive, though the physical findings were very similar to those seen in disseminated sclerosis. One patient (Case 20) had a relapsing neurological illness which cleared up completely after 21 months, and has shown no further neurological disability during the 10 years following. In Case 21 an encephalomyelic illness has been followed by transient neurological incidents of a very minor nature during the subsequent 12 years.

Case 18. Acute encephalitic illness with loss of consciousness and lymphocytic pleocytosis in the spinal fluid, leaving a disabling non-progressive and non-recurrent neurological syndrome with signs strikingly similar to those of advanced disseminated sclerosis.

This 21-year-old miner was admitted to hospital in January 1942. He had been ill for 10 days with fever, sore throat, diarrhoea, and vomiting. Four days before admission he complained of intense headache, and became mentally confused, with slurred speech. During the 48 hours preceding admission he became drowsy, and had repeated episodes of deep unconsciousness without convulsion. On admission he was stuporose, but could be roused with difficulty. The pupils were unequal and sluggish, speech was indistinct, and there was nystagmus in all directions, and profound ataxia and gross spontaneous tremor, most marked in the arms. The right arm and leg were weak, without any reflex abnormality. There was no fever or meningism; the spinal fluid contained 25 lymphocytes per c.mm., but was otherwise normal. Consciousness became clear within 10 days. Improvement occurred during the subsequent month, but there was no further change during the next six months; the patient was then discharged from hospital dysarthric, bedridden, and ataxic, with gross tremor of the head and limbs. The abdominal reflexes were absent, but the plantar responses were flexor. Until a month before his discharge he had repeated episodes of double vision, without strabismus, lasting a few days at a time. On re-examination in 1952 there had been no new symptoms, and no exacerbations of the original symptoms, during the subsequent 10 years. The signs were similar to those described on his discharge from hospital in 1942—gross tremor of the head, scanning dysarthria, and profound ataxia of all limbs and trunk. He could sit up, but could not stand unaided. There was no ophthalmoplegia, and the pupils and fundi were normal, but there was gross nystagmus in all directions. With the exception of absent abdominal reflexes his deficit was entirely cerebellar; there was no spasticity, true loss of power, sensory impairment, or intellectual change.

Case 19. Subacute neurological illness with disseminated signs, without remission or relapse, but with severe residual disability until death 14 months later.

This previously healthy 45-year-old woman gradually became unsteady on her legs seven weeks before admission to hospital in 1934. Two weeks later she developed blurred vision in both eyes, slurring speech, and weakness and tremor of the right hand. Examination on admission revealed recent impairment of memory and attention with some disorientation, dysarthria of cerebellar type, nystagmus, continuous tremor of the head, spasticity and ataxia in the right arm, absence of the left abdominal reflexes, increased deep reflexes, more marked in the left leg but present also in the right, and flexor plantar

TABLE V
Residual or Relapsing Disability

<i>Case number</i>	<i>Age (years)</i>	<i>Aetiological factors</i>	<i>Clinical features</i>	<i>Cerebro-spinal fluid</i>	<i>Follow-up</i>	<i>Subsequent history</i>	<i>Signs on re-examination</i>
18	21	M Sore throat, vomiting, and diarrhoea for 1 week	Headache, delirium, stupor; recurrent coma. Unequal pupils. Nystagmus, ataxia, and tremor of limbs; weakness of left arm and leg. No meningism. Return of full consciousness after 10 days. Dysarthria; diplopia	25 cells per c.mm.	10 years	6 months later was bedridden with dysarthria, ataxia, and gross tremor. No pyramidal signs apart from absent abdominal reflexes. No sensory loss	Dysarthria, nystagmus, ataxia, gross tremor of head. No pyramidal signs apart from absent abdominal reflexes. No sensory loss
19	45	F 0	Unsteadiness of legs for several weeks. Later impairment of vision, dysarthria, nystagmus, tremor of head, spastic right arm and left leg. Impairment of memory and disorientation	9 cells per c.mm.	..	Death 14 months later. She had remained bedridden but developed no new signs	..
20	39	M 'Febrile cold' 5 days before	Rapidly recovering paraplegia, some weeks before. Then severe paraplegia, diplopia, dysarthria, and some weakness of arms. Left abdominal reflexes absent. Rapid recovery	Normal	10 years	Repeated transient illnesses—headache and coma or fleeting paraplegia—during next 21 months. No recurrence afterwards	No abnormal findings except absent ankle-jerks
21	25	F 'Febrile cold' and bronchitis for 1 week	Headache, transient aphasia, and weakness of legs. Emotional lability, dysarthria. Signs of right hemiparesis. Absent abdominal reflexes on both sides. Sensation normal. Recovery in 7 days	12 cells per c.mm.	12 years	Recurrent prostrating headaches with vomiting of decreasing severity. Transient diplopia followed a cold on 7 occasions	Absent abdominal reflexes. Increased reflexes in right leg with extensor plantar response

responses. The spinal fluid was normal except for a slight lymphocytic pleocytosis (nine cells per c.mm.). There was little improvement, and she died 14 months after the onset of the illness. She remained bedridden until her death, but developed no new neurological symptoms. She was depressed rather than euphoric, and there were no sphincter disturbances. No details are available as to the mode of death. Her relatives stated that she 'just wasted away'; death was certified as due to disseminated sclerosis.

Case 20. Relapsing encephalomyelitis, with intermittent symptoms during the course of 21 months. Complete recovery, with absence of ankle-jerks as the sole abnormal finding 10 years later.

This 39-year-old silica works foreman had a febrile cold with severe pains in the limbs nine weeks before admission. The day after the onset of these symptoms his legs became weak and he was unable to walk. There is no record of physical signs at that time, and he recovered within a week. Seven weeks later there was a recurrence of similar but more severe symptoms following five days of coryza, fever, and generalized muscular pains. On this second occasion, in addition to more pronounced weakness of the legs, there were diplopia without strabismus, slurred speech, and weakness and numbness of the arms, without impairment of consciousness or of sphincter control. Within three days his limbs began to improve, but the diplopia and dysarthria showed little improvement on admission to hospital two weeks later. On examination at this time (May 1940) he was alert, with no pyrexia, but with slurred speech and absence of the left abdominal reflexes. There were no other abnormal signs, and the spinal fluid was normal. Ten days later symptoms and signs had completely disappeared, and he was discharged from hospital. Three weeks after discharge he retired to bed with headache and a left facial paralysis of lower-neurone type, from which he recovered in five weeks. During the following 18 months he was subject to repeated episodes of neurological illness, which occurred without any recognizable preceding infection, and with decreasing frequency. They often took the form of sudden loss of consciousness, preceded by headache and associated with pyrexia, but without epileptic features. Such episodes lasted usually for an hour or two, but on one occasion for six days. At other times the attacks consisted of sudden weakness of one or both legs, of insidious onset, with depression of reflexes and equivocal plantar responses, which lasted for periods up to one day. Twenty-one months after the onset of his illness the condition cleared up entirely. On re-examination in 1952 he stated that during the subsequent 10 years his only disability had been intermittent attacks of dyspepsia from a gastric ulcer, which had been present for 30 years. There was no neurological disability, and the only abnormal finding in the nervous system was absence of both ankle-jerks.

Case 21. Acute neurological illness of one week's duration with dysarthria, emotional lability, and focal signs, clearing completely, but with recurrent headaches and transient episodes of diplopia during the subsequent 12 years.

This 25-year-old woman, who was at the time nursing a three-months-old infant, was admitted to hospital in 1940. A week before admission she had developed a febrile coryza with bronchitis, followed five days later by severe generalized headache. The day before admission she lost her speech completely for several hours, although consciousness was clear and she knew exactly what she wished to say. Early on the day of admission she developed almost complete paralysis of the legs, without sphincter disturbance. On examination she was irritable and very labile emotionally, but without disorientation or impairment of consciousness. Speech was slurred, the pupils

TABLE VI
Myelitis with Good Recovery

<i>Case number</i>	<i>Age (years)</i>	<i>Sex</i>	<i>Aetiological factors</i>	<i>Clinical features</i>	<i>Cerebro-spinal fluid</i>	<i>Follow-up</i>	<i>Subsequent history</i>	<i>Signs on re-examination</i>
22	15	F	Minor illness with 'spotted' face 9 days before	Sudden weakness of right leg with numbness of left leg. Nystagmus. Sensory loss below groin; increased reflexes and extensor plantar responses in both legs. Rapid recovery. Walked normally after 2 months	Normal	11 years	Occasional paraesthesiae in limbs at night	Absent abdominal reflexes. Increased reflexes in right leg. Plantar responses flexor
23	36	F	0	Headache, fever, retention of urine, and flaccid paraplegia, with sensory loss below T6. Nystagmus. Weakness and tremor of hands	15 cells per c.mm.	16 years	Able to walk after 6 months. Required catheterization for 8 months. Returned to work after 1 year. Afterwards had occasional retention of urine	Absent abdominal reflexes. Increased knee- and ankle-jerks. Plantar responses flexor and ankle-jerks. Plantar responses brisk. Vibration sense impaired in left foot
24	19	M	0	Gradual development of weakness and numbness of legs. Signs of transverse lesion of cord at T10: sensory loss, spastic legs, extensor plantar responses	13 cells per c.mm.	16 years	Returned to work after 6 months. Later complained of occasional paraesthesiae in feet	Increased knee- and ankle-jerks; plantar responses flexor. Abdominal reflexes brisk. Vibration sense impaired in left foot

were unequal and sluggish, and there were signs of a right hemiparesis, with an extensor plantar response, and symmetrical absence of the abdominal reflexes. There was no sensory impairment or fever, and the spinal fluid contained 12 lymphocytes per c.mm. Recovery was rapid. Within 48 hours speech was normal, the emotional symptoms had disappeared, and the left abdominal reflexes had returned. Six days later she was discharged from hospital without disability, and with an extensor plantar response on the right as the only abnormal finding. Re-examined in 1952, she stated that since the illness 12 years previously she had suffered from recurrent, prostrating, generalized headaches, with vomiting, of decreasing frequency and severity. She described these attacks as migraine; there were no classical features, and no relevant past or family history, of this condition. Twelve months after the illness, in 1942, she had had an episode of double vision, lasting for three days and not associated with strabismus. This recurred six times during the subsequent nine years, usually when she was 'off colour' or suffering from a definite coryza, but was unrelated to her attacks of headache or to menstruation. Two years before re-examination she was delivered of a second child without incident. Examination revealed symmetrical absence of the abdominal reflexes, and increased deep reflexes in the right leg with an extensor plantar response. There were no abnormal findings in the cranial nerves, no signs of disturbed cerebellar function, and no sensory change.

Transverse myelitis

Of 10 patients who had transverse myelitis without encephalitic symptoms, three made a good recovery with trivial disability, minor residual signs, and no further neurological incidents during periods of 11, 15, and 16 years respectively.

Case 22. Acute transverse myelitis following a possible exanthem. A partial transverse cord lesion improved rapidly, leaving trivial residual disability and minor signs 11 years later.

Ten days before admission to hospital this 15-year-old girl had a minor illness with a swollen, spotted face. The day before admission she developed weakness of the right leg and tingling sensations in the left leg. Examination revealed nystagmus, absent abdominal responses, weakness of the right leg with loss of proprioceptive sensation, normal motor power in the left leg with impairment of superficial sensation up to the groin, and generalized increase of the deep reflexes in the lower limbs, with bilateral extensor plantar responses. The spinal fluid was normal. Two days later the power in the right leg returned, and after 11 days sensation was normal. She was walking normally after two months, and served as a driver in the Auxiliary Territorial Service. Ten years after the onset of the illness she had a normal confinement. On re-examination 11 years after her illness her sole disability was occasional paraesthesiae in all the limbs at night. The abdominal responses were absent, and the knee- and ankle-jerks on the right were increased. The plantar responses were flexor.

Case 23. Acute transverse myelitis, with complete recovery except for occasional difficulty in micturition 15 years later.

This 36-year-old woman was admitted to hospital in June 1937 with an illness of two weeks' duration characterized by headache, fever, dysuria progressing to retention of urine, and a flaccid paraplegia, with sensory loss below the waist, which had gradually increased in severity during the seven days preceding admission. There was no disturbance of consciousness. Examination revealed nystagmus, weak and tremulous hands, and signs of an almost

TABLE VII
Myelitis with Residual Disability

<i>Case number</i>	<i>Age (years)</i>	<i>Sex</i>	<i>Aetiological factors</i>	<i>Clinical features</i>	<i>Cerebro-spinal fluid</i>	<i>Follow-up</i>	<i>Subsequent history</i>	<i>Signs on re-examination</i>
25	18	F	0	Numbness and paralysis of legs, retention of urine, and constipation. Signs of severe transverse lesion of cord at T10	Normal	..	No improvement.	..
26	37	M	Scarlet fever	Numbness and paraesthesiae below waist with weakness of legs. Not admitted to hospital	..	14 years	Returned to work after 6 months. Afterwards backache, stiffness of legs, and frequency of micturition	Spastic paraparesis with extensor plantar responses. No sensory loss
27	44	F	0	Complete paralysis of right leg; weakness of left leg. Girdle pains. Knee- and ankle-jerks depressed, plantar responses extensor. Sensory loss below L1 on left side	Normal	16 years	Slow improvement for 18 months. Then persistent weakness of right leg. Able to walk short distances	Weakness of right leg. Impaired superficial sensation in left leg. Increased deep reflexes with bilateral extensor plantar responses
28	13	F	0	Sudden complete paraplegia with incontinence, absent deep reflexes, and extensor plantar responses. Sensory loss below T2. Nystagmus and weakness of left arm	Normal	17 years	Sphincters normal after 4 months. Returned to work after 12 months. Afterwards persistent limp, and pain on walking far	Slight nystagmus to right. Increased reflexes in both legs, with bilateral extensor plantar responses. Weakness of left leg. Superficial sensory impairment up to groin

complete transverse cord lesion at T 6. The spinal fluid showed a moderate lymphocytic pleocytosis. Recovery began within four weeks. The patient was walking six months later, but had to be catheterized regularly for eight months in all. The sensory signs improved more quickly than the motor weakness, and it was 12 months from the onset of the illness before she returned to work. Two years after discharge from hospital she was delivered of a healthy child without incident. On re-examination in 1952 she had no spontaneous complaints except that once or twice a year, particularly if she allowed her bladder to become distended, she developed retention of urine and had to be catheterized. The only abnormal signs on full examination were absent abdominal reflexes and some exaggeration of knee- and ankle-jerks, without spasticity and with flexor plantar responses.

Case 24. Transverse myelitis of gradual onset, with slow but complete recovery. Sixteen years later there had been no recurrence, and there were only trivial residual symptoms and signs.

A 19-year-old miner noticed weakness and numbness of the legs one month before admission; the disability gradually increased until he was unable to walk. On admission to hospital in 1936 he showed signs of a severe transverse lesion at the level of T 10 with spastic legs, extensor plantar responses, and marked impairment of all forms of sensation. The spinal fluid contained 13 lymphocytes per c.mm., but was otherwise normal. Improvement was rapid. The level of sensory loss gradually receded at its upper and lower limits. A week later superficial sensation was everywhere normal, and two weeks after this he was discharged from hospital with considerable improvement of power. He returned to work six months after the onset of the illness. On re-examination in 1952 his only symptom was occasional 'pins and needles' in both feet. He was working steadily as a coal cutter; the only abnormal signs remaining were increased reflexes in the legs and impairment of vibration sense in the left foot. The plantar responses were flexor, and the abdominal reflexes brisk.

In four patients transverse myelitis was followed by appreciable or severe residual disability, without further neurological incidents, during periods of six, 14, 16, and 17 years respectively. The first of these patients died as a result of chronic urinary infection.

Case 25. Severe transverse myelitis, showing little improvement and causing death six years later from chronic urinary infection.

Three weeks before admission to hospital in 1938 this 18-year-old girl had pain in the right eye, which lasted for 24 hours and was not accompanied by impairment of vision. A week later she developed severe pain in the buttocks, numbness and paralysis of the legs, retention of urine, and constipation. Examination revealed signs of a severe transverse cord lesion at T 10, with a transient pulmonary infiltration in the left lower lobe. During eight months in hospital this patient showed little improvement except the resolution of the pneumonitis and the disappearance of her girdle pains. She survived six years without improvement. Constipation and incontinence of urine persisted, and she died six years later as a result of intractable pyelonephritis with hypertension and uraemia.

Case 26. Transverse myelitis following scarlet fever, with some residual disability and persisting physical signs.

In 1938 this 37-year-old man had a severe attack of scarlet fever. As the rash faded he developed tingling and numbness below the waist, and on leaving

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his bed he found himself almost unable to walk. The patient was not admitted to hospital, and no lumbar puncture was carried out. The condition slowly improved, and he was able to return to business duties within six months. Since that time he has had backache, stiffness and weakness of the legs on walking more than half a mile, and frequency and precipitancy of micturition. Re-examination in 1952 revealed a spastic paraparesis with extensor plantar responses, but without sensory change.

Case 27. Asymmetrical transverse myelitis with moderately disabling sequelae, showing residual motor and sensory deficit. No further neurological illness during the subsequent 16 years.

In 1936 this 44-year-old woman suddenly lost the use of her right leg, and developed weakness of the left leg and dysuria, on rising from bed one morning. There was considerable pain in a girdle distribution. Examination revealed profound weakness of the right leg, with diminution of knee- and ankle-jerks and impairment of proprioceptive sensation. On the left there was superficial sensory loss up to the level of L 1. The plantar responses were extensor; the spinal fluid was normal. Improvement began one week later, and she was able to walk within three weeks. Improvement continued for 18 months, after which the condition became stationary. On re-examination in 1952 the patient was still moderately disabled. She could walk only half a mile, the right leg was weak, the knee- and ankle-jerks were increased on both sides, both plantar responses remained extensor, and there was impairment of superficial sensation in the left leg below the knee.

Case 28. Acute transverse myelitis, with good recovery, but with some residual disability 17 years later.

This 13-year-old girl was admitted to hospital in May 1935 with an acute transverse myelitis of sudden onset, with no history of preceding infection. Complete paraplegia, with absent deep reflexes and extensor plantar responses, was accompanied by weakness of the left arm, nystagmus, incontinence of urine and faeces, loss of superficial sensation below T 2, and some peripheral diminution of vibration sense. The spinal fluid was normal. Recovery began within three weeks, and four months later bladder and bowel functions were almost normal and she could stand with assistance. Improvement continued, and she returned to work 12 months after the onset. On re-examination in 1952 there was no evidence of subsequent neurological incidents. She still walked with a limp, and had pain in the left leg if she walked more than a mile. There was slight nystagmus to the right, increased reflexes in the left arm without disability, spastic weakness of the left leg, exaggerated deep reflexes in both lower limbs, more marked on the left, and bilateral extensor plantar responses. Superficial sensation was still distinctly impaired up to the groins, but proprioceptive sensation was normal. The patient had worked until her marriage, and had had a healthy baby two years ago without incident.

In three patients transverse myelitis was followed by subsequent neurological illness. The first of these patients had a further myelitic lesion after an interval of 15 years, with excellent recovery of function; the second had a severe transverse myelitis, without recovery of function, nine years after a very mild similar episode; and the last showed equivocal evidence of recent emotional instability, and possibly increasing dysarthria, 17 years after partial recovery from a myelitic lesion.

Case 29. Partial transverse myelitis resulting in an incomplete Brown-Séquard syndrome, clearing rapidly but followed 15 years later by a partial transverse lesion of the spinal cord, with almost complete but much less rapid recovery.

This previously healthy 45-year-old woman was admitted to hospital in 1936. She gave a history of 10 days' progressive ascending weakness in the right leg and a similarly ascending sensation of heat and numbness in the left leg. Examination at this time revealed flaccid weakness of the right leg, with sluggish knee- and ankle-jerks, and an extensor plantar response on the right. In the left leg there was loss of superficial sensation up to the groin; there was no impairment of proprioceptive sensation in either leg. The abdominal responses were retained, and the spinal fluid was normal. Recovery was rapid, and she was discharged from hospital six days later without residual disability or sensory loss, but with an extensor plantar response on the right. For 15 years she was perfectly well, but in 1951 she suddenly developed ascending sensations of tingling and numbness in both legs, with unsteadiness on her feet. She stated that the sensory change on this occasion was quite different from that felt in the left leg 15 years previously: on the present occasion the legs 'felt like india rubber'. Examination at this time showed absence of the abdominal reflexes, increased deep reflexes in the right leg, plantar responses extensor on the right and equivocal on the left, and bilateral loss of vibration sense up to L 1. A blood count was normal. This second attack cleared up gradually and completely during the course of four months. On re-examination in 1952, 12 months after the disappearance of symptoms of the second episode, there was no subjective disability, and the only abnormal findings were some increase of the reflexes in the right leg and an extensor plantar response on this side; the abdominal reflexes were normal.

Case 30. Transverse myelitis originally clearing rapidly and completely, and recurring nine years later, leaving on this occasion a permanent and almost complete transverse cord lesion.

In 1932 this 33-year-old miner developed pain across the shoulders, followed by an acute partial transverse lesion of the cord. The legs were very weak, and numbness extended to the waist. Recovery was remarkably rapid, and he was able to walk within six days and returned to work within a month. Nine years later (1941) an initially identical illness was characterized by a more profound transverse cord lesion at T 7. All reflex activity below this level disappeared, the patient had a temperature of 101° F., and the spinal fluid contained 27 lymphocytes per c.mm. but was otherwise normal. During the first three days in hospital the upper level of sensory loss ascended to T 5, but there was no further change, and no evidence of recovery on his discharge from hospital six months later. Re-examination 11 years after the second episode revealed signs of an apparently complete transverse lesion of the spinal cord at T 5. There had been no further neurological episodes, and there were no abnormal signs above this level. His paralysis remained flaccid, and there had been no recovery of sensation. He remained totally disabled.

Case 31. Acute transverse myelitis with slow partial recovery, and a residual syndrome resembling disseminated sclerosis and showing equivocal recent deterioration.

This woman, the 34-year-old mother of two children, was admitted to hospital in 1935. Two weeks previously she had noticed numbness and coldness in the toes. This feeling spread up the legs, and a week later she fell to the ground with an acute flaccid paraplegia, and hesitancy of micturition gave

place to retention of urine. There was no disturbance of general health, neck stiffness, headache, or fever. Examination revealed spastic paraparesis, with absent abdominal responses, exaggerated deep reflexes in the lower limbs, extensor plantar responses, and complete analgesia with partial loss of other forms of sensation up to the costal margin. The thigh muscles showed persistent clonic twitching for three days. In spite of an early ascent of the level of sensory loss to the nipple line and the disappearance of the knee- and ankle-jerks, improvement began within six weeks, and spontaneous control of the bladder returned. Fifteen weeks after the onset she recovered some movement in the toes, and from this time very slow improvement continued. In 12 months she had made a fair recovery. She was able to walk about the house and for short distances outside, but there was still marked numbness and some weakness in the legs, with hesitancy and frequency of micturition. Her spinal fluid was several times examined and showed no pleocytosis, but a raised protein content (90 mg. per 100 ml.) was found three weeks after the onset. When seen in 1952 at the age of 51 years, she stated that there had been little change during the subsequent 16 years. Three years after her discharge from hospital she had been delivered of a third child without incident. There was still occasional hesitancy and precipitancy of micturition; she was doing all her own housework, but was still reluctant to travel away from home, and did not walk more than a quarter of a mile unless it was necessary. On examination there was patchy loss of superficial sensation below the nipple line, more marked on the right side, and accompanied by impairment of vibration sense in the right leg. The abdominal reflexes were absent, and the knee-jerks very brisk. The ankle-jerks were almost extinct, and the plantar responses extensor. Although she made no spontaneous complaint, it was noticed that her speech was slurred. Her husband stated that this slurring had been noticed since her discharge from hospital, though he thought it had possibly become more marked during recent years. For three years he had also noticed an increasing emotional lability: the patient would laugh immoderately at, or would be depressed by, trivial incidents which would previously have left her unmoved. The optic disks were thought to be pale, but ophthalmological examination (Mr. Stafford Maw) revealed no scotomata and 'no evidence that the visual pathways have ever been affected'.

Acute neurological illness with visual failure

In three patients classified in the hospital records as cases of acute encephalomyelitis, visual failure was a prominent feature. The first patient showed fair recovery, with no further incident during the course of 19 years, the second complete recovery maintained for 15 years. The third patient, after a partial recurrence of symptoms seven months after excellent recovery from the initial attack, showed no further symptoms during a period of 15 years. The third case was a typical example of Devic's disease (neuromyelitis optica); the other two cases in this group would certainly be similarly described by many neurologists. The reasons for their inclusion in the present series are given in the discussion.

Case 32. Acute neurological illness with headache, mental confusion, bilateral retrobulbar neuritis, and a transverse spinal cord lesion in the dorsal region. Good recovery of vision and moderate recovery of cord lesion, without recurrence during the subsequent 19 years.

This 43-year-old woman was admitted to hospital in August 1933 with an acute illness of two weeks' duration. The illness began with intense generalized

headache and mental confusion, followed by fever, pain in the eyes, rapid loss of vision, progressive weakness of the legs, and dysuria progressing to retention of urine. Examination revealed a bilateral retrobulbar neuritis with almost complete loss of vision, and a severe transverse cord lesion at T 10, with absence of the abdominal reflexes, flaccid limbs, extensor plantar responses, and profound loss of all forms of sensation. The spinal fluid showed a moderate lymphocytic pleocytosis. Vision returned in two weeks, and when the patient was discharged from hospital six months later power had begun to return in the legs. Twelve months after the onset of the illness she was able to do her own housework, though weakness and stiffness of the right leg and frequent incontinence of urine persisted. Seen again in 1952, she stated that precipitancy of micturition remained invariable and incontinence frequent, and that she still had difficulty in getting about because of weakness and stiffness of the right leg. She complained also of patches of numbness in the legs, and of occasional precipitancy of bowel action. Although there was no subjective complaint as regards vision and she could read without glasses, ophthalmological examination confirmed the presence of slight optic atrophy. No scotomata were found, the only defect being a moderate general depression of the fields. Examination also revealed a marked increase of deep reflexes in the right arm and leg, absence of the abdominal reflexes, bilateral extensor plantar responses, and loss of superficial sensation over the right tibia.

Case 33. Subacute neurological illness with bilateral retrobulbar neuritis at the age of six years with complete recovery.

This six-year-old boy was admitted to hospital in 1937. Two months previously he had had a major epileptic convulsion, followed by transient weakness of the right side. Ten days later a similar attack was associated with dysphasia, which persisted for 36 hours. The child was then apparently well for two months, but five days before admission he was noticed to have difficulty in recognizing objects, and within two days became completely blind. The only other symptom noticed by the parents at this time was frequent muscle twitching of capricious distribution. On examination consciousness was clear, and there was no meningism or complaint of headache. Almost total blindness was due to a bilateral optic neuritis with marked swelling of the optic disks. The only other sign in the nervous system was an equivocal and slightly extensor plantar response on the right. There was no pyrexia or meningism, but the spinal fluid showed a moderate lymphocytic pleocytosis. Improvement was rapid, and within 13 weeks all symptoms had disappeared and the visual acuity was 6/12 (right) 6/9 (left). When seen in 1952 at the age of 21 years, the patient stated that apart from scarlet fever, measles, and appendicitis there had been no subsequent illness, and he was in perfect health without subjective symptoms. The optic fundi were normal, visual acuity remained as recorded 15 years previously, and examination of the visual fields showed no scotomata.

Case 34. Syndrome of neuromyelitis optica, with good recovery and partial recurrence 12 months later. No neurological incidents during the ensuing 15 years.

This 21-year-old man was admitted to hospital in 1936. Six days previously he had developed dimness of vision. Within three days complete blindness ensued, and was associated with retention of urine. There were no encephalitic symptoms, and no meningism. Twenty-four hours before admission to hospital headache, neck stiffness, and fever became apparent, and he developed signs

of a transverse lesion of the spinal cord at T 6. On admission to hospital examination revealed a severe transverse lesion in the mid-dorsal region, with retention of the abdominal reflexes, depression of the deep reflexes in the lower limbs, and equivocal plantar responses. There was marked loss of superficial sensation below the level of the lesion, but proprioceptive sensation was only slightly impaired. Moderate swelling of the optic disks was present, and there was profound visual loss, with only faint perception of light. The spinal fluid contained 95 lymphocytes per c.mm. Improvement began within two weeks, the temperature and spinal fluid becoming normal. Visual and spinal-cord symptoms improved concurrently. Power in the legs improved first, sensation became normal, and within six weeks he had regained control of the bladder, the papillitis had resolved, and he was able to read. Nine weeks after the onset he was able to walk without assistance, and vision had returned to normal. He returned to work 40 weeks after the onset of the illness. Seven months later (1937) there was an acute recurrence of visual failure. He was almost completely blind for two weeks, but there was no recurrence of cord symptoms.

When seen in 1952 he stated that his only disabilities, which had been noticed ever since the first episode, were some difficulty in reading with the left eye alone and occasional frequency of micturition. On examination the only abnormal findings were a bilateral, apparently primary, optic atrophy, with central depression in the right field, and on the left a similar depression with marked loss of the peripheral nasal field and a large ill-defined pericaecal scotoma. There was also fine nystagmus at the extremes of lateral deviation. The only remaining sign of the spinal cord lesion was an equivocal plantar response on the right.

Discussion

The report given in the present paper includes patients showing purely myelitic and purely encephalitic features, and others exhibiting mixed or encephalomyelic syndromes. If justification is required for reporting these cases together under the clinical grouping of acute disseminated encephalomyelitis, it may be found in the following considerations. Any facet of this polymorphic illness (encephalitis, myelitis, encephalomyelitis, encephalomyleoradiculitis) may be encountered in identical clinical contexts—9 to 12 days after primary Jennerian vaccination, on the fourth to sixth day of measles, or rapidly following apparently non-specific upper respiratory infections. Secondly, minimal encephalitic symptoms are seen fairly often in transverse myelitis, and in some cases frank encephalitis follows either rapidly or in a subsequent relapse. Thirdly, histological study of the small number of adequately reported cases in which death occurred during the acute phase of transverse myelitis reveals predominantly perivascular cellular infiltration and myelinoclasia, findings generally similar to those seen in more diffuse cases of acute disseminated encephalomyelitis; and in such cases of transverse myelitis the pathological finding of asymptomatic encephalitic changes is not rare (Davison and Keschner, 1933). The attempt to synthesize a clinical entity from material so polymorphic is clearly open to criticism. Wilson (1940), for example, doubted whether acute disseminated encephalomyelitis could be clinically differentiated with any confidence either from abortive encephalitis lethargica or from acute disseminated sclerosis. On these grounds, and in view of the absence of any

identifiable common aetiological factor, he stated that 'it is more than doubtful whether any self-contained disease to which this title can apply has a real existence'. On grounds which are chiefly histopathological Marburg (1906, 1942) grouped together acute encephalomyelitic illnesses following exanthemata and those which occur apparently spontaneously, as a special form of acute disseminated sclerosis (*parencephalomyelitis periaxialis scleroticans*). Ferraro (1937, 1944) also subscribed to the unitary theory, and regarded disseminated sclerosis as in essence a chronic relapsing form of acute disseminated encephalomyelitis. He postulated an allergic origin for this whole group of demyelinating diseases, a theory which has been extended to relate them to the 'allergic' encephalomyelitis produced by the injection of brain emulsion and adjuvants into experimental animals (Kabat, Wolf, and Bezer, 1947; Morgan, 1947; Lumsden, 1949). Ford (1952) accepted the occurrence, 'spontaneously' or after non-specific infections, of acute disseminated encephalomyelitis identical with that seen after exanthemata. This author, however, widened his conception of neuromyelitis optica to include any such cases in which there is recurrence of symptoms, and considered that the whole of this second group may possibly represent atypical forms of disseminated sclerosis. Nevertheless general considerations, as well as study of the present cases, lend strong support to the view originally put forward by Redlich (1927), Brain, Hunter, and Turnbull (1929), and McAlpine (1931), and more recently persuasively argued by van Bogaert (1950), that acute disseminated encephalomyelitis is a clinical entity, or—if devotion to semantics has rendered the term otiose—that this group of patients exhibits a recognizable illness, variable in its clinical manifestations but constant in its natural history and its biological significance. According to this view it is possible to formulate generally valid diagnostic criteria of acute disseminated encephalomyelitis (McAlpine, 1931) and, as remarked by Redlich (1927) and stressed by Guillain (1931), the prognosis in such cases is entirely different from that with which we are familiar in disseminated sclerosis.

The final court of appeal in such disputes is usually the histopathologist. In this instance, however, unanimity among the authorities is lacking. Marburg's claims (1906, 1942) rest on dubious pathological grounds; some, at least, of his cases of acute disseminated sclerosis would now be described on pathological as well as on clinical grounds as cases of acute disseminated encephalomyelitis. Ferraro's hypothesis (1937, 1944) of histopathological unity among the group is also strongly disputed by other authorities (Kolb, 1950). There is no doubt as to the striking similarity of the lesions in post-vaccinal encephalomyelitis to those seen in similar cases after measles (Turnbull and McIntosh, 1926), and such lesions appear to be identical with those which occur in encephalomyelitis after non-specific infections (Greenfield, 1930; Grinker and Bassoe, 1931). Lumsden (1949) has demonstrated the histological similarity between the changes seen in such cases and in the encephalomyelitis produced in experimental animals by the injection of brain emulsions, while the allergic nature of the experimental condition has been further supported by its inhibition by cortisone (Kabat, Wolf, and Bezer, 1951, 1952). The pathological relationship,

however, between the lesions of human and experimental acute disseminated encephalomyelitis and those of acute disseminated sclerosis is much more questionable. In spite of striking variations in the histological pattern of inflammatory changes in acute disseminated encephalomyelitis—variations which may well depend on the duration and severity of the disease—there is no dispute as to their predominantly perivascular distribution. Recent claims that the more massive demyelinating lesions of disseminated sclerosis are also in essence perivascular (Cournand, 1930; Putnam 1935, 1937; Ferraro, 1937) run counter to the careful histopathological studies reported earlier by Anton and Wohlwill (1912), Dawson (1916), and Wohlwill (1928), and to the histopathological distinctions drawn between acute disseminated encephalomyelitis and acute disseminated sclerosis by Hallervorden (1929). Dow and Berglund (1942) denied a predominantly perivascular incidence, and both Lumsden (1949) and Kolb (1950) conceded the close relationship between human and experimental encephalomyelitis, but considered the changes by no means analogous with those seen in acute disseminated sclerosis. The main contentions of those who oppose on pathological grounds the unitary theory, that all these conditions represent phases of an apparently allergic encephalomyelitis, appear valid. While individual sections of tissue from cases of disseminated sclerosis may give the impression that the characteristic lesions are perivascular, serial sections reveal that the vessels are in fact found to run alternately in and out of well-defined plaques, in contrast to the appearance in acute disseminated encephalomyelitis, where the vessel is seen to be surrounded by a sleeve of inflammation and myelinoclasia throughout its length. The relative immunity of the axis cylinders and of the grey matter in acute disseminated sclerosis, and the tendency to massive fibrous gliosis in the chronic form of the disease, are further examples of differences which cannot convincingly be attributed to variations in the duration of a single pathological process. Further evidence in the same direction is offered by the observation of Herkenrath (1935) and Schaltenbrand (1938), who have shown that cases coming to autopsy after recovery from post-vaccinal and other forms of acute disseminated encephalomyelitis reveal either the persisting perivascular lesions typical of the disease, or almost complete resolution, but not the lesions of disseminated sclerosis. In summary, while pathological evidence supports a close relationship between the various forms of acute disseminated encephalomyelitis in man and 'allergic' encephalomyelitis in the experimental animal, evidence that these diseases are histopathologically related to disseminated sclerosis is unconvincing. The paucity of adequate pathological reports on unequivocal cases of acute disseminated sclerosis, and the limited pathological repertoire of the central nervous system in response to widely variable noxae, render a firm conclusion on this hypothetical relationship premature.

Clinical evidence is in our opinion less equivocal, and clearly establishes the separate identity of acute disseminated encephalomyelitis. Even of the examples described by Thygesen (1949) and van Bogaert (1950), 14 out of 29 and 11 out of 19 patients respectively remained free from further neurological

illness for periods of many years. In the case of the former author, the subsequent development of cerebro-vascular accidents and symptoms of chronic lethargic encephalitis in several of the other patients raises some doubts as to the level of diagnostic accuracy brought to bear in the initial encephalomyelitic illnesses. Thygesen appeared to favour the unitary theory of the demyelinating diseases, and to imply that attempts to draw fine clinical distinctions between encephalomyelitis and acute disseminated sclerosis are in any case probably fruitless; such an attitude would almost certainly influence the initial selection of cases for follow-up study, and hence the proportion of patients ultimately developing signs of disseminated sclerosis. In van Bogaert's (1950) series, four of 19 patients who had acute disseminated encephalomyelitis are described as subsequently developing 'classical' disseminated sclerosis, but unfortunately clinical details of these cases are lacking in an otherwise very fully documented study. The significance of these observations is in the last resort uncertain. They establish without doubt the existence of cases of acute encephalomyelitis which by reason of their excellent long-term prognosis are clinically distinct from disseminated sclerosis. The fact that a proportion of patients whose condition is diagnosed as acute disseminated encephalomyelitis may subsequently prove to be suffering from disseminated sclerosis admits of two possible explanations. Either acute disseminated encephalomyelitis may on occasion develop into disseminated sclerosis, or they are different diseases, the clinical differentiation of which may present great and sometimes insuperable difficulty.

Consideration of the present cases lends strong support to the second interpretation. Not one of the 27 patients surviving an acute encephalomyelitic illness in this series developed unequivocal evidence of disseminated sclerosis during periods extending up to 19 years, and averaging 14 years in the 22 patients alive in 1952. In Cases 18 and 19 the physical findings were identical with those often seen in disseminated sclerosis. In the former case, however, the condition followed an acute encephalomyelitic illness, since which 10 years have elapsed without further neurological incident. Case 19 is typical of the group of cases variously described as 'acute disseminated sclerosis' or 'subacute encephalomyelitis', and illustrates the virtual impossibility of definitive clinical diagnosis in this small minority of cases. It is, however, where there is 'dissemination in time' (relapse or recurrence), as well as anatomical dissemination, that the problem of differentiation from multiple sclerosis arises most acutely. There were three unequivocal instances of *relapse*. Cases 5 and 6 developed fatal encephalitic relapses 10 days and 20 weeks respectively after myelitic illnesses. Again, similar cases have been reported as examples of 'acute disseminated sclerosis', and the autopsy finding of subacute perivascular inflammatory and demyelinating changes has been cited to indicate the pathological identity of acute disseminated sclerosis and acute disseminated encephalomyelitis. Such cases are, however, by no means unknown after exanthemata, or in early childhood at ages when disseminated sclerosis is highly unlikely (Brain, 1930). In our view both clinical and pathological evidence indicates that, like many such examples described elsewhere as 'acute disseminated sclerosis', Cases 5 and 6 are in fact instances

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of subacute disseminated encephalomyelitis. Similar considerations apply to Case 20, which exhibited relapsing neurological incidents of decreasing severity during an illness of 21 months' duration, ending in complete recovery maintained throughout the subsequent 10 years. In the five instances of *recurrence* there is clearly room for differences of opinion, but in our view the history in all is more compatible with the original diagnosis than with that of disseminated sclerosis. In Cases 29 and 30 second attacks of transverse myelitis occurred after intervals of 15 and 9 years respectively. In the former patient excellent recovery occurred from both episodes, but in the latter the second attack of probably necrotic myelitis left grave non-progressive disability. Evidence of lesions outside the spinal cord developed in neither case, and there appears to be no more reason to label these cases as disseminated sclerosis than to diagnose this disease in Case 34, in which a partial recurrence of the syndrome of neuromyelitis optica, seven months after the initial classical attack, was followed by good recovery maintained without incident during the subsequent 15 years. The relationship of neuromyelitis optica to acute disseminated encephalomyelitis and to disseminated sclerosis is discussed below. Cases 21 and 31 are admittedly equivocal. In the former a definite respiratory illness preceded the acute onset of a neurological syndrome characterized by aphasia, headache, and florid neurological signs, which cleared almost completely within a few days—a syndrome characteristically encephalomyelic. Subsequent episodes of diplopia, often arising in relation to minor infective illnesses, persisted for 12 years, but re-examination at the end of this period revealed no evidence suggesting progressive neurological deficit except disappearance of the abdominal reflexes. In Case 31 fair recovery from transverse myelitis left non-progressive disability, and the only evidence slightly in favour of disseminated sclerosis has been the onset of emotional lability 14 years later, at the age of 48 years. It is possible that Cases 21 and 31 are in fact instances of disseminated sclerosis, but the evidence in favour of such a view is somewhat tenuous, and the natural history in both cases far from typical.

Whatever their pathological relationship, the difference in natural history and prognosis between the cases described in the present paper and those with which we are familiar as cases of disseminated sclerosis is such as to render differentiation between acute disseminated encephalomyelitis and acute episodes of disseminated sclerosis of considerable practical importance. In our view the diagnostic criteria formulated by McAlpine (1931) are reliable, and permit accurate diagnosis in the majority of cases. They are worth elaborating here. First, any impairment of consciousness in an acute episode of disseminated sclerosis is very uncommon indeed, and although we have personal experience of one patient with unequivocal disseminated sclerosis who has marked clouding of consciousness in frequent tetraplegic exacerbations, impairment of consciousness in an initial illness is strongly in favour of the diagnosis of encephalomyelitis. Secondly, meningism, a temperature above 100° F., and severe shooting pains in the limbs or elsewhere are uncommon even in acute episodes of established disseminated sclerosis. Headache is of more equivocal significance.

Thirdly, there are some symptoms common in disseminated sclerosis which are relatively rare in acute disseminated encephalomyelitis: these are diplopia, unilateral retrobulbar neuritis, and euphoria. Conversely, there are some signs which are commonly found in encephalomyelitis but are rare in disseminated sclerosis: these are loss of deep reflexes and retention of the abdominal reflexes in the presence of extensor plantar responses. The occurrence of levels of superficial sensory loss in disseminated sclerosis is of course much less frequent than impairment of proprioceptive sensation, but it is well recognized that such loss can occur (Keschner and Malamud, 1924). Such levels tend, however, to be transient and less well-defined than those commonly seen in encephalomyelitis; and although transverse myelitis may occur in the course of disseminated sclerosis, especially in advanced cases, it is excessively rare, if indeed it ever occurs, as an initial symptom of that disease. The natural history of relapse and recurrence in encephalomyelitis is also, in our experience, entirely different from that with which we are familiar in disseminated sclerosis. Recurrences of encephalomyelitis are essentially phasic, and, as pointed out by van Bogaert (1950) and demonstrated in several of our own cases, such recurrences tend to reactivate lesions and to revive physical signs which were present in the initial illness, while the prognosis of these exacerbations is that of encephalomyelitis and not that of acute exacerbations of disseminated sclerosis. In our experience recovery from such recurrences tends to be more complete and more rapid than is usual in episodes of disseminated sclerosis, and to be a matter of days rather than weeks. The insidious progression of disability, which can be correlated with the massive fibrous gliosis seen in disseminated sclerosis, and which is as characteristic a feature of that disease as are acute exacerbations, is entirely lacking.

In embarking on the present study our hope was to find some clue as to aetiological factors in disseminated sclerosis, which are perhaps the central problem of contemporary neurology. It has served rather to emphasize the differences between acute disseminated encephalomyelitis and the chronic disease, the causation of which remains entirely obscure. In our view there is, however, growing evidence that acute disseminated encephalomyelitis represents a non-specific allergic reaction of the nervous system to varying antigens, chiefly of bacterial or virus origin, though possibly of other kinds as well. The pathological evidence in favour of this view consists chiefly in the apparent relationship already noted between the human disease and the experimental 'allergic' encephalomyelitis produced by injection of sterile brain emulsion in the experimental animal. Some of the clinical evidence in favour of this view presented by Miller (1951) can be amplified in the light of the work presented above. The fact that acute encephalomyelic syndromes in every way similar to those described above are occasionally encountered in serum sickness, following a variety of sterile prophylactic inoculations, and in rare instances of angio-neurotic oedema, is one such piece of evidence. The occasional coincidence with human encephalomyelitis of other syndromes clearly of hypersensitive origin, such as urticaria, purpuric eruptions, and acute glomerulonephritis, points in the same direction. One further feature to which we would draw particular

attention is related to recurrent encephalomyelitis. Recurrence of acute disseminated encephalomyelitis is almost unknown in patients whose initial illness follows one of the specific fevers. When such recurrences exceptionally occur they may follow other exanthems, and may be considered to indicate an allergic constitutional factor. No unequivocal recurrences were encountered in a series of 27 further cases of post-vaccinal encephalomyelitis recently reported (Miller, 1953b). It appears both from the literature and from personal experience that recurrence tends to occur chiefly in cases following non-specific minor infections, usually of the upper respiratory tract, in which the development of lasting immunity is known to be exceptional, and in which repeated antigenic insults furnish a possible pathogenetic mechanism. We have at present under observation a family of three children, each of whom has had several episodes of unequivocal encephalomyelic illness following coryzal attacks. These episodes apparently respond to adrenocorticotrophic hormone, and the regular administration of antihistamine drugs appears to afford some protection against the neurological complications of these frequently recurring banal infections.

Views as to the aetiology of acute disseminated encephalomyelitis have changed with the years. At first it was attributed to the acquisition of neurotropic properties by the virus of the initiating infection. Further virus studies rendered this view untenable, and its place was taken by the hypothesis that the initiating infection potentiated a second virus already in the tissues. No such virus has ever been demonstrated and, since the histopathological changes of the disease are quite unlike those seen in any known virus infection, this view also has been largely discarded. If it is objected that the postulation of an allergic aetiology adds little to the view that the conditions are 'toxic', it must be conceded that, from the patient's point of view at any rate, allergy is merely one form of toxicity. The distinction between the two is, however, more than terminological; if recent claims for the efficacy of adrenocorticotrophic hormone in the human disease (Ligterink, 1951; Garrison, 1952; Miller, 1953a) are confirmed, it may have therapeutic and prophylactic implications. In patients such as Case 14, in whom transverse myelitis followed body-chilling, pathogenesis as well as aetiology may be different. Wilson (1940) commented on this relationship, and we have seen another example. The onset in such cases is usually rapid, within hours of exposure, but the disability may be subacutely progressive (Miller, 1953a). This fact, and the observation that paralysis may be provoked by chilling the animal experimentally infected with poliomyelitis virus (Levinson, Milzer, and Lewin, 1945), indicate that the possibility of a combined physical and inflammatory mechanism cannot be excluded, though the fact that chilling appears to lead to myelitic rather than to encephalitic illness may be taken to favour a direct effect of the physical agent, possibly mediated through some reflex vascular disturbance. Among other points of clinical interest is the observation that encephalomyelitis in relation to exanthemata (and therefore presumably also in relation to less clearly definable infections) may occasionally precede manifest symptoms of the initial infection, as in Case 9, in which encephalomyelitis appeared during the

incubation of varicella. For this reason the terms 'para-infective' or 'para-exanthematous' may be considered more accurate than 'post-infective' or 'post-exanthematous' in describing this group of encephalomyelitic illnesses. The association of polyradicular lesions with encephalomyelitis (Case 13) is also worthy of note: such lesions, which may be local or generalized, are not encountered in disseminated sclerosis, and raise the question of an aetiological relationship between the cases under discussion and instances of acute infective polyneuritis or polyradiculoneuritis (Guillain-Barré syndrome), which frequently follows infection and is an occasional sequel both of prophylactic inoculation and of exanthemata.

Neuromyelitis optica. Cases 32, 33, and 34, though classified in the hospital records and described here as instances of acute disseminated encephalomyelitis, presented the syndrome of neuromyelitis optica (Devic's disease), and the first and third cases are typical examples of this condition. Their inclusion here is open to criticism; neuromyelitis optica is regarded by many as a variant of disseminated sclerosis, and by some as a separate disease entity. The literature of the condition is confused by the application of the term to a wide variety of clinical syndromes, including not only the classical picture of transverse myelitis with bilateral retrobulbar neuritis, but also examples of retrobulbar neuritis without myelitis, myelitis without retrobulbar neuritis, and indeed almost any instance of relapsing encephalomyelitis (Ford, 1952). The conception of neuromyelitis optica is obscured also by the tendency of earlier authors in particular to describe only cases coming to autopsy, and thereby to perpetuate the fiction that the ultimate mortality of the syndrome is in the region of 100 per cent. Recent workers, however, and in particular Kohut and Richter (1945), Stansbury (1949), and Scott (1952), have not limited their studies to post-mortem material, but have also followed up partial syndromes of a similar nature and cases of recovery. Their papers leave no room for doubt as to the clinical distinction between neuromyelitis optica and disseminated sclerosis, and lend considerable support to a much closer relation between Devic's syndrome and acute disseminated encephalomyelitis, of which in our view the syndrome is a clinical variant, and to which it is certainly closely related. The present small series of cases illustrates further points in this connexion.

Histopathological evidence is again somewhat equivocal. Hassin (1937) considered the appearances in neuromyelitis optica distinct both from those of disseminated sclerosis and from those of acute disseminated encephalomyelitis. Ferraro (1937) regarded all three conditions as phases of a single disseminated demyelinating process. Several examples of Devic's syndrome coming to autopsy have been described as showing the histopathological appearances of disseminated sclerosis, as for example the case of Alajouanine, Hornet, Thurel, and Rossano (1935). In all such cases which we have traced, however, the disease was of 'acute' type with early demise, often from a recurrence of frankly neuromyelitic symptoms. The histopathological findings in such cases are as equivocal as in the instances of 'acute disseminated sclerosis' previously noted, and are similarly compatible with a diagnosis of subacute disseminated en-

encephalomyelitis. While the statement of Alajouanine and his colleagues that neuromyelitis optica is 'an anatomico-clinical syndrome which may be produced by various infections, and in particular by acute disseminated sclerosis' may well be correct, and while there is no theoretical reason why the combination of bilateral retrobulbar neuritis and transverse myelitis may not occasionally occur in disseminated sclerosis, we have encountered no recorded case in which Devic's syndrome ensued as an incident in the course of established disseminated sclerosis, or in which the syndrome was followed by the slowly and intermittently deteriorating course typical of the chronic disease. On the whole the recorded pathological findings favour a closer relation to encephalomyelitis than to disseminated sclerosis. The patches of demyelination are diffuse and ill defined, while both myelinolysis and cellular infiltration are predominantly perivascular. Grey matter is not spared, and all the neural elements are involved in lesions of an acuteness and intensity foreign to disseminated sclerosis, frequently necrotic and sometimes leading to cavitation.

Study of the natural history of neuromyelitis optica leaves little doubt as to its close relationship to acute disseminated encephalomyelitis. The age incidence of the two conditions is similar, and quite unlike that of disseminated sclerosis. Neuromyelitis optica has been encountered at all ages from six to 66 years, with a greatest incidence in the fourth and fifth decades. Preceding acute infections are common, and though they are most commonly non-specific upper respiratory or pharyngeal infections, the syndrome may occasionally follow a specific fever such as measles (Brain, 1951). The immediate and remote prognosis of Devic's disease is also similar to that of acute disseminated encephalomyelitis. Death often occurs within weeks or months of the onset, or may be delayed at the most for two or three years. On the other hand complete or almost complete recovery, with no subsequent neurological symptoms for many years, is common, as shown by Scott (1952) and as exemplified in our own cases. When recurrence does occur, as in Case 34, it is a recurrence of neuromyelitis optica, which may be partial as in this instance, or severe and fatal. In either case the prognosis is that with which we are familiar in neuromyelitis optica, and not that of disseminated sclerosis. Devic himself (1894) recognized that this is not a 'pure' syndrome, and that cases otherwise typical are sometimes complicated by cerebral symptoms and signs arising outside the optic pathways and the spinal cord. Cases 32 and 33 in the present series show features suggesting encephalitic involvement, as reported also by Wilson (1940), Ford (1952), and others, while widespread histopathological changes in the neuraxis have been demonstrated, for example, by Putnam and Forster (1942). The absence in neuromyelitis optica of euphoria, and the relative rarity of nystagmus and of changes in the spinal-fluid Lange curve, are minor features which argue against the identity of the syndrome with disseminated sclerosis, but are in no way incompatible with a close relationship to acute disseminated encephalomyelitis. If our hypothesis as to the nature of the latter disease is valid, the point at issue is of more than terminological importance.

Summary

This paper is based on the study of 34 cases of acute disseminated encephalomyelitis occurring in Newcastle upon Tyne between 1932 and 1942. In a consecutive hospital series of 29 cases there were seven fatalities, and six of these were instances of essentially encephalitic illness with profound coma. Of the 27 survivors in the total series, five subsequently died without evidence of recurrent or progressive neurological symptoms. In two cases the signs of the initial illness were strikingly similar to those encountered in disseminated sclerosis, and although the first of these was in our opinion almost certainly a case of acute disseminated encephalomyelitis, the second, which was fatal within a little over a year, was a possible instance of acute disseminated sclerosis. Twenty-two patients still living were re-examined in 1952. Although a number were still disabled by non-progressive residual disability, no patient in this group had developed evidence of typical disseminated sclerosis. There were in the whole series three instances of relapse, and five of recurrence, of encephalomyelic illness. In two of the recurrent cases it is remotely possible that disseminated sclerosis is the correct diagnosis.

The view is put forward that acute disseminated encephalomyelitis and disseminated sclerosis are separate diseases which may occasionally be difficult to distinguish, but in which distinction is important because of their entirely different prognoses. The aetiology of disseminated sclerosis remains quite obscure, but clinical and pathological evidence is presented in favour of the view that acute disseminated encephalomyelitis represents a non-specific allergic reaction of the nervous system to various antigens usually infective in origin. Such a hypothesis considers the human condition closely analogous to the encephalomyelitis which may be produced experimentally in various animals by parenteral injections of brain emulsion, a view which may have important therapeutic implications.

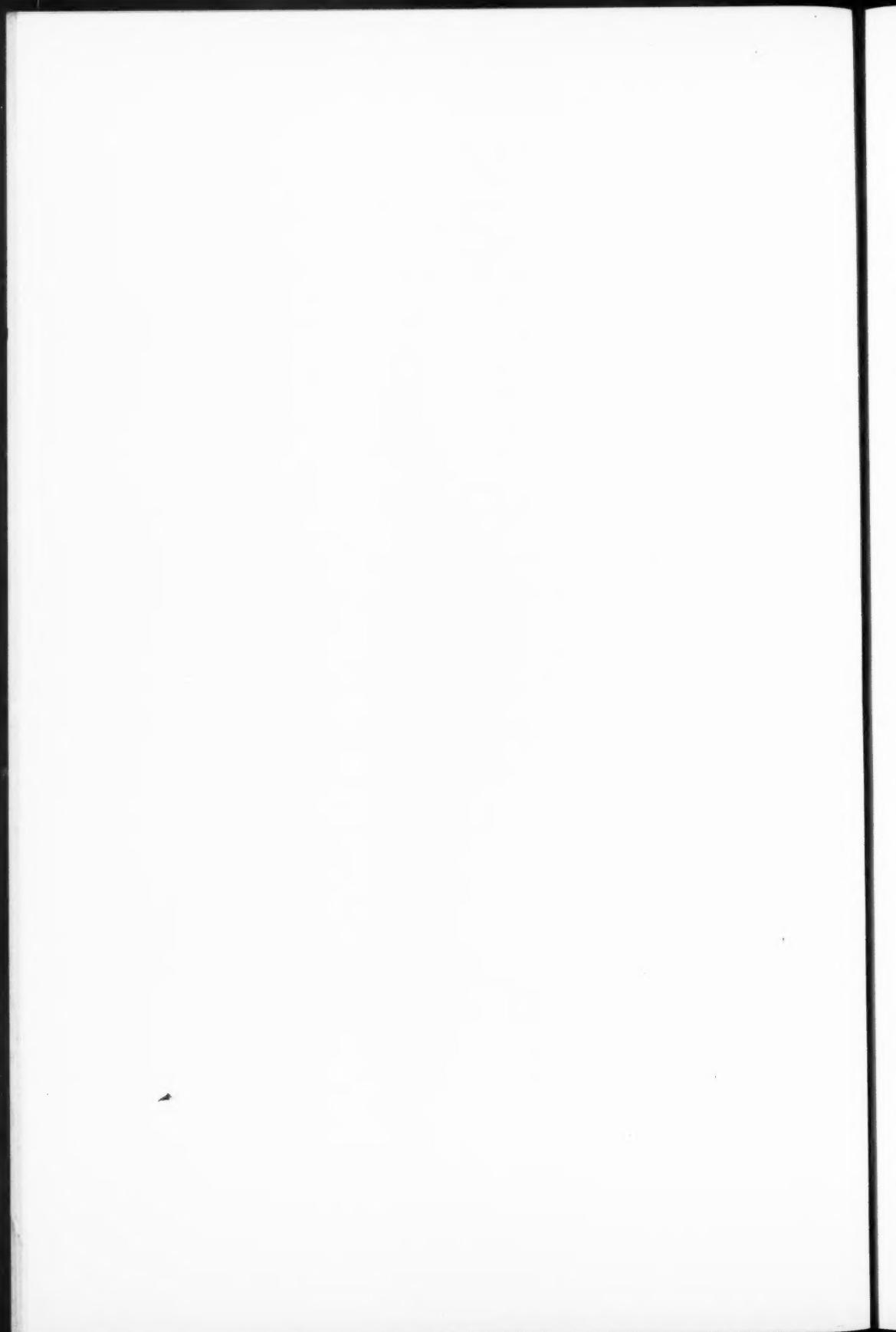
The syndrome of neuromyelitis optica is briefly considered, with three illustrative cases. Evidence is put forward indicating that the condition is entirely separate from disseminated sclerosis, in which its occurrence appears to be not fully authenticated, and that it is closely related to acute disseminated encephalomyelitis.

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THE CAUSES OF POST-PRANDIAL ATTACKS OF PALPITATION AND WEAKNESS AFTER GASTRIC OPERATION¹

BY W. HAMILTON SMITH, RUSSELL FRASER, K. STAYNES, AND
J. M. WILLCOX

(From the Department of Medicine, Postgraduate Medical
School of London)

With Plates 28 and 29

PARTIAL gastrectomy for chronic peptic ulcer is now commonly performed with an expectation of under two per cent. mortality and a recurrence rate of about three per cent. (Tanner, 1952), but its success makes important the avoidance of any other disabilities which may follow the operation. A liability to post-prandial attacks of weakness and palpitation is perhaps the commonest of these sequels, and such attacks have been attributed to various causes. We have studied a series of patients suffering from such attacks in the hope of defining the disorders which cause them and the means of alleviation and prevention. The post-prandial attacks of weakness and palpitation which may develop after gastric operations are of two types, early and late, due to different causes, but clinically distinguishable almost solely by their time of onset. Early attacks occur during or within half an hour of meals; late attacks occur from one and a half to three hours after meals (Adlersberg and Hammerschlag, 1947). The late attacks are due to hypoglycaemia (Evensen, 1942); most observers believe that the early attacks are due to rapid gastric emptying, and call them 'dumping' attacks.

Though Billroth's first successful gastrectomy was performed in 1881, the first clear account of post-prandial attacks developing after gastric operations was given by Hertz in 1913: 'A sensation of fullness which occurs during each meal, which may be so unpleasant that the amount of food taken is progressively diminished and a considerable loss of weight may finally occur.' Such attacks occurring after gastro-enterostomy were called 'dumping' attacks by Ryle (1934) and Snell (1937), as were similar attacks occurring after gastrectomy by Eusterman and Balfour (1935), Alvarez (1939), and Devine (1940). In 1933 Beckermann described rather similar post-prandial attacks, also developing after gastro-enterostomy and gastrectomy, which he ascribed to hypoglycaemia from reactive hyperinsulinism. These hypoglycaemic attacks were studied further by Christlieb (1938), Evensen (1942), Adlersberg and Hammerschlag (1947, 1949) and Zollinger and Hoerr (1947). The last two groups of authors

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both pointed out that these attacks were distinguishable from 'dumping' attacks by their later onset after meals and their relief with sugar. A liability to either form of attack after gastrectomy is not rare; the reported incidence varies between 3 per cent. (Lake, 1948) and 75 per cent. (Muir, 1949), but for the most part ranges between 5 and 19 per cent. (Custer, Butt, and Waugh, 1946; Visick, 1948; Wells and Welbourn, 1951; Capper and Butler, 1951; Milstein, 1951). The reported incidence, as a rule, concerns dumping attacks, but often the distinction between the types of attack has not been made. Late, or hypoglycaemic, attacks are much rarer than dumping attacks, and usually tend to persist (Adlersberg and Hammerschlag, 1947, 1949), but are less disabling (Evensen, 1942; Muir, 1949; Capper and Butler, 1951). The attention given by different workers to eliciting the symptoms has varied. The type of operation performed has some influence on the frequency of the attacks. Dumping attacks have been said by some observers to occur with equal frequency after operations for duodenal and for gastric ulcer (Watson, 1947; Capper and Butler, 1951); others have said that they occur more frequently after operations for duodenal ulcer (Muir, 1949; Pulvertaft, 1952). They are uncommon after gastro-enterostomy (Eusterman and Balfour, 1935; Snell, 1937; Capper and Butler, 1951), and after gastrectomy they are more frequent the more radical the resection (Perman, 1947; Wells and Welbourn, 1951). After gastrectomy with gastroduodenal anastomosis (Billroth I) such attacks are rare (Perman, 1947; O'Neill, 1950; Capper and Butler, 1951; Gray-Turner, 1951; Waugh, 1951; Wells and Welbourn, 1951; Pulvertaft, 1952). The inclusion of a valve in the gastrojejunal anastomosis (Polya) has been said to reduce the incidence (Finsterer and Cunha, 1931; Morley and Roberts, 1928-9; Maingot, 1940; Custer, Butt, and Waugh, 1946; Lake, 1948; Mimpriss and Birt, 1948; O'Neill, 1950; Milstein, 1951; Doyle, 1951) but this fact has been denied (Capper and Butler, 1951). Though it has been claimed that dumping attacks are rare after total gastrectomy or gastrectomy for carcinoma (Jordan, 1941), this statement has been more frequently denied (Brain, 1951; Wells and Welbourn, 1951; McDonough and O'Neil, 1951). Rarely attacks of dumping (Moore, Chapman, Schulz, and Jones, 1947; Smith, 1951) and of hypoglycaemia (Johnson, 1951; Weinberg, Kraus, Stempfien, and Wilkins, 1951) follow vagotomy.

Patients who suffer from dumping attacks after gastric operations usually have other disabilities. Probably all patients who have dumping attacks of more than minor severity are also under-weight (Hertz, 1913; Eusterman and Balfour, 1935; Berkman and Heck, 1945; Wollaeger, Comfort, Weir, and Osterberg, 1946; Adlersberg and Hammerschlag, 1947; Muir, 1949; Capper and Butler, 1951), though not all patients who are under-weight after gastrectomy suffer from dumping attacks. This loss of weight must be partly due to the associated disorders which many patients show, such as avoidance of large meals which induce severe attacks (Snell, 1937; Adlersberg and Hammerschlag, 1947; Muir, 1949; Wells and Welbourn, 1951), diarrhoea (Hertz, 1913; Eusterman and Balfour, 1935; Berkman and Heck, 1945; Muir, 1949; Capper and Butler, 1951), and defective absorption (Wollaeger, Comfort, Weir, and Osterberg,

1946; Wells and Welbourn, 1951; Brain, 1951). Defective intestinal absorption in such cases has been ascribed to intestinal hurry (Lee, 1951; Glazebrook and Welbourn, 1952). Steatorrhoea may be found after gastric operations, though, unlike the diarrhoea, it is not specially associated with dumping attacks (Rekers, Pack, and Rhoads, 1943; Wollaeger, Comfort, Weir, and Osterberg, 1946; Mimpriss and Birt, 1948; Lee, 1951; Glazebrook and Welbourn, 1952; Brain, 1951). Glazebrook and Welbourn (1952) found that hexamethonium bromide increased fat-absorption when it was defective, as well as decreasing the intestinal hurry in patients with dumping attacks. Defective intestinal absorption has also been attributed to retention of bile and pancreatic juice in the afferent loop (Mimpriss and Birt, 1948). While bilious vomiting may frequently be associated with the dumping attacks, either complication may occur alone (Visick, 1948; Irvine, 1948; O'Neill, 1950; Capper and Butler, 1951; Glazebrook and Welbourn, 1952); both disabilities have been attributed to kinking of the afferent loop (Capper and Butler, 1951; Wells and Welbourn, 1951) or to neurosis or to both factors (Muir, 1949). Other disabilities which may develop after gastrectomy are microcytic anaemia (Morley and Roberts, 1928-9; Gordon-Taylor, Hudson, Dodds, Warner, and Whitby, 1928-9; Lublin, 1931; Vaughan, 1932; Hartfall, 1934; Larsen, 1934; Lake, 1948; Church and Hinton, 1942; Meyer, Schwartz, and Weissman, 1941; Watson, 1947; Muir, 1949; Wells and Welbourn, 1951), macrocytic anaemia (Rowlands and Simpson, 1932; Larsen, 1934; Hartfall, 1934; Meyer, Schwartz, and Weissman, 1941; Brain, 1951; Lee, 1951), and vitamin deficiencies (Muir, 1949; Welbourn, Hughes, and Wells, 1951; Brain, 1951); but they are not more frequent with than without dumping attacks.

Hertz's (1913) original ascription of dumping attacks to 'too rapid drainage of the stomach' has been generally accepted, though not proved (Louria, 1928; Pallin, 1932; Ryle, 1934; Eusterman and Balfour, 1935; Devine, 1940; Schwartz, Reingold, and Necheles, 1942; Bockus, 1944; Custer, Butt, and Waugh, 1946; Watson, 1947; Perman, 1947; Visick, 1948; Irvine, 1948; Paulson and Gladstones, 1948; Alvarez, 1949; Muir, 1949; Machella, 1949; Wells and Welbourn, 1951). After gastro-enterostomy or gastrectomy the stomach is seen radiologically to empty more rapidly than normal (Pendergrass, Ravdin, Johnston, and Hodes, 1936; Strauss, Strauss, Levitsky, Scheman, Seidmon, Arens, Meyer, and Necheles, 1937; Ingelfinger, 1944; Mimpriss and Birt, 1948; Schechter and Necheles, 1949; Butler and Capper, 1951; Milstein, 1951; Singmaster and Engel, 1951); but a still more rapid emptying when dumping attacks occur has not been demonstrated, probably because a routine barium meal is unsuited to discriminating between rapid and precipitate emptying. The alternative explanations which have been offered for dumping attacks do not, however, seem likely. They have been ascribed to kinking and distension of the afferent loop (Finsterer and Cunha, 1931; Lake, 1937; Maingot, 1940; Marshall, 1944-5; Ingelfinger, 1944; Ogilvie, 1947; Mimpriss and Birt, 1948; Steinberg, 1949; Muir, 1949), to 'hyperglycaemic shock' (Glaessner, 1940), to gastritis (Lublin, 1931), to jejunitis (Konjetzny, 1932; Porges, 1947), and to drag on the

lesser omentum from inadequate gastric support (Butler and Capper, 1951). Dumping symptoms seem to result from excessive jejunal stimulation; they have been produced by various abnormal jejunal stimuli such as the entry of iced water, hypertonic solutions, large volumes of water (Clute and Bell, 1941; Alvarez, 1949; Doyle, 1951), or distension by a balloon (Muir, 1949; Machella, 1949; Brain, 1951), though Zollinger and Hoerr (1947) and Butler and Capper (1951) failed to produce them by this last means. Rapid introduction of food via a jejunostomy stoma can produce the attacks (Alvarez, 1949; Doyle, 1951; Smith, 1951). They are associated with jejunal hyperactivity (Custer, Butt, and Waugh, 1946; Machella, 1949), as Glazebrook and Welbourn (1952) showed by both radiological and kymographic evidence. The last-named authors found that hexamethonium bromide could prevent both this hyperactivity and the dumping symptoms. No adequate explanation has been offered of the way in which jejunal hyperactivity leads to palpitations and weakness. A predisposition, existing before operation, to develop such attacks has been suggested, due either to neurotic instability (Adlersberg and Hammerschlag, 1947, 1949; Visick, 1948; Tanner, 1948; Schechter and Necheles, 1949; Pulvertaft, 1952), or to gastro-intestinal hypermotility (Eusterman and Balfour, 1935; Snell, 1937; Bockus, 1944); but in view of the relevance of the type of operation, predisposition can only be one factor.

The oral glucose-tolerance test after gastrectomy or gastro-enterostomy shows a rapid rise and fall of blood-sugar levels (Lapp and Dibold, 1932; Kalk and Meyer, 1932; Wöhrle, 1937; Evensen, 1942; Aldersberg and Hammerschlag, 1947; Gilbert and Dunlop, 1947; Schechter and Necheles, 1949; Moore, 1950), due probably to rapid gastric emptying, since duodenal intubation reproduces the effect. The late post-prandial or hypoglycaemic attacks have usually been ascribed to reactive hyperinsulinism produced by the rapid absorption of carbohydrate (Beckermann, 1933; Farris, Ransom, and Coller, 1943; Bockus, 1944; Gilbert and Dunlop, 1947; Muir, 1949; Wells and Welbourn, 1951). Although such attacks occur only after oral glucose, and not after intravenous glucose (Farris, Ransom, and Coller, 1943; Gilbert and Dunlop, 1947), the increase of blood-sugar after oral glucose is no more rapid in these patients than with others who have had gastrectomy (Evensen, 1942; Wöhrle, 1937), so that the attacks evidently depend on some additional factor not yet fully defined (Lawrence, 1947). Barnes (1947) reported that such patients showed increased insulin-sensitivity, but did not explain its presence. Similar post-prandial hypoglycaemic attacks may occur without gastric operations (Wilder, 1940; Conn, 1940), especially in patients with duodenal ulcer (Christlieb, 1938; Bockus, 1944; Lawrence, 1947). In view of this fact, damage to the vagus (Weinberg, Kraus, Stempien, and Wilkins, 1951) seems an unlikely cause. The post-prandial hypoglycaemia has been attributed vaguely to nervous disposition and autonomic instability (Christlieb, 1938; Straaten and Hünermann, 1939; Schechter and Necheles, 1949; Jefferson, Phillips, Levine, and Necheles, 1949-50). Wilder (1940) and Adlersberg and Hammerschlag (1947, 1949) found evidence of associated neurosis in an unduly large proportion of patients subject

to such attacks. Glucose-tolerance tests before operation have not been found helpful in picking out patients liable to such attacks (Moore, 1950), though Adlersberg and Hammerschlag (1949) suggested this method.

Method of Study

We chose for study groups of patients who, after operation, had typical and persistent attacks of weakness and palpitation, occurring early or later after meals, and we contrasted them with another group of patients who had had similar operations, and were chosen because they were free from symptoms, and also with normal subjects and with a patient who had a jejunostomy. The preceding operation in most, but not all, cases was gastrectomy (see Appendix II). At least nine months had elapsed since the operation when the patients were chosen. The groups of 'gastrectomy' patients studied were as follows:

Group I. With no symptoms	nine patients
Group II. With dumping attacks	seven "
Group III. With both dumping and hypoglycaemic attacks	two "
Group IV. With hypoglycaemic attacks	eight "

Gastric emptying and intestinal activity were evaluated radiologically both with a standard barium meal and with a barium-glucose mixture, and also by oral glucose-tolerance tests; carbohydrate metabolism was studied by oral and intravenous glucose-tolerance tests and intravenous insulin-tolerance tests after adequate dietary preparation. We also searched for physiological and biochemical changes during the early post-prandial attacks, by close clinical observation and regular blood-sampling after a standard meal taken in a standard posture; comparable observations were also made after introducing these standard meals by a jejunostomy stoma, after meals other than the standard, after meals following hexamethonium bromide, and after drugs such as adrenaline given without meals. The standard meal is described elsewhere (Smith, 1951). Fuller details of these methods of study are given in Appendix I; Appendix II shows the criteria used in recognizing typical persistent attacks, and the details of the operations undergone. For defining the normal range of results of some of the carbohydrate tests, results already published were used (Evensen, 1942; Fraser, 1943). Certain medical and surgical methods of treating dumping attacks were also assessed in the case of some patients.

Results

I. *Gastric emptying and intestinal activity*

1. *Gastric emptying.* Table I summarizes the findings as regards gastric emptying. With the standard barium meal, the finding of an empty stomach at 10 minutes was taken as evidence of very rapid gastric emptying (Plates 28 and 29, Fig. 6, *a* to *h*). With the barium-glucose meal equivalent significance was given to the finding of an empty stomach at 60 minutes. With the barium-glucose meal the stomach became empty at between 90 and 180 minutes in five

out of seven patients who had had similar operations and had no symptoms, and in all of five patients who had hypoglycaemic attacks. In the other two patients who were free of symptoms the stomach emptied more rapidly with this test, but not with the standard barium meal, of which a considerable bulk was retained after 10 minutes. All but one of the patients who had dumping attacks showed rapid emptying by both these radiological criteria; the exception was

TABLE I
Gastric Emptying-rate in the Four Groups of Gastrectomy Patients

Results of three methods of assessment

Group	Number of patients showing very rapid gastric emptying		By oral glucose-tolerance test	
	By standard barium meal (stomach empty in 10 min.)	By barium-glucose meal (stomach empty in 60 min.)	Area A over 50*	'Absorption index' over 600†
I. With no symptoms	0/7	0/7	2/9	0/9
II. With dumping attacks	4/5	5/6	6/7	7/7
III. With dumping and hypoglycaemic attacks	2/2	2/2	2/2	2/2
IV. With hypoglycaemic attacks	1/3	0/5	1/8	2/8

* Units used for measures of area A: 1 = 10 minutes, and also 1 = 10 per cent. of fasting level of blood-sugar.

† 'Absorption index' = sum of 15-, 30-, and 45-minute blood-sugar values in mg. per 100 ml.

the patient who had had vagotomy. But when the latter patient was given a colloidal preparation of barium some of it was visible in the transverse colon at 30 minutes, and after a barium-glucose mixture the stomach was virtually empty at 60 minutes, and the barium was visible in the ascending colon; so that, with ordinary meals, the stomach probably emptied rapidly. The familiar difficulties were encountered in measuring gastric emptying radiologically. Individual patients varied from day to day in their responses, presumably owing to their nervous state, even with a standardized radiological technique and standard meal. Further, from a shadow, it was possible to assess only approximately the volume of gastric contents. Hence we turned to oral glucose-tolerance tests, with the patient in the sitting posture, since the test conditions could be more easily standardized.

Glucose is absorbed by the small intestine (Miller, 1944; Karel, 1948), and gross alterations in the rate of gastric emptying have been found to be reflected in the blood-sugar curve (Evensen, 1942; Moore, 1950). Other factors can, of course, modify the rate of increase of blood-sugar in an oral glucose-tolerance test (Cori, 1931); but when primary disease of the liver or intestine is unlikely this test provides an index of gastric emptying. In our patients, therefore, we used the speed and extent of the initial rise in blood-sugar after oral glucose as

an index of the rate of absorption, and hence of combined gastric emptying and intestinal motility; quarter-hourly blood samples during the first hour are required for this purpose. This test, using a 15 per cent. solution of glucose, also proved useful in our patients because it readily induced their dumping attacks. To obtain an index of the initial rise of the curve, blood-sugar values have been charted as percentages of the fasting level, and the area enclosed by the curve

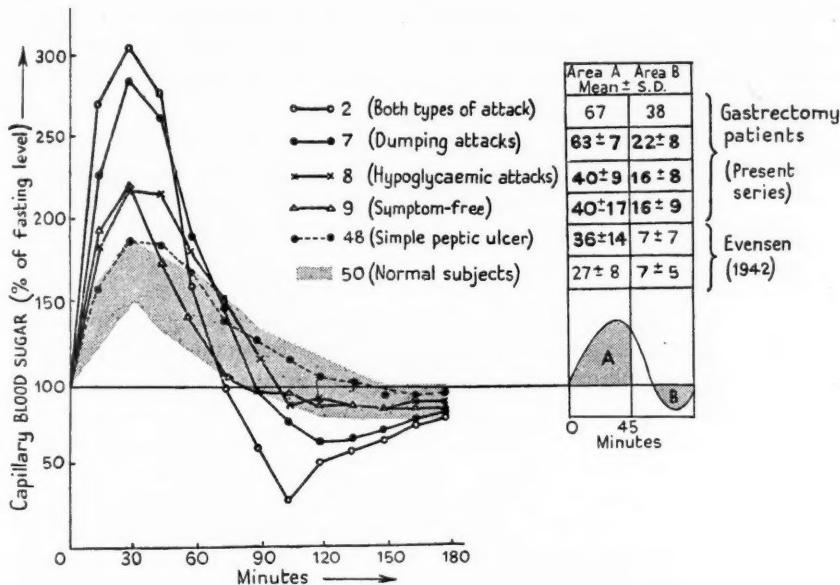


FIG. 1. Results of oral glucose-tolerance tests.

Note the initial rises, indexed by area *A*, which are very rapid only in the groups with dumping attacks, and rapid in all the other gastrectomy groups. The curve in the group with hypoglycaemic attacks resembles that in the symptom-free group after gastrectomy. These accelerated initial rises probably reflect the increased rate of gastric emptying. The area values shown in bold type are significantly different from those of the normal group. One unit of area = 10 per cent. of fasting level = 10 minutes.

from 0 to 45 minutes has been measured (area *A*, Fig. 1). The differences noted below between the initial rises in blood-sugar levels in the different groups of patients are evident from inspection of the mean curves, and are all statistically significant when area *A* is used as an index of the initial rise. From Fig. 1 it is evident that the patients who had dumping attacks showed a steeper rise than any of the other groups. With the symptom-free group the initial rise was still abnormally rapid, but distinctly less so; the peptic ulcer patients who had had no operation showed a still slower, but yet rapid increase of blood-sugar. Thus these curves confirm the radiological finding of very rapid or precipitate gastric emptying only among the patients who had dumping attacks, and of merely rapid gastric emptying among all other gastrectomy patients, and to a lesser degree among some peptic ulcer patients who had had no operation. As shown in Table I and Fig. 5, the test showed some overlap between the groups; but area *A* was over 50 in eight out of nine patients with dumping attacks, and in only

three out of 17 of the other gastrectomy patients. As a simpler 'absorption index' the sum of the three blood-sugar values at 15, 30, and 45 minutes may be used. By this index aggregate values of over 600 mg. per 100 ml. suggest precipitate emptying; such high values were found in all nine patients who had dumping attacks, in only two out of eight patients who had hypoglycaemic attacks, and in none of the nine gastrectomy patients who were free of symptoms. Among the patients liable only to hypoglycaemic attacks (Table I) gastric emptying-rates were found equivalent to those of the symptom-free group. Although the oral glucose-tolerance test may be a less reliable index of gastric emptying in the patients liable to hypoglycaemia, similar results were given by the barium-meal studies.

2. *Intestinal activity.* On fluoroscopy, the two patients who had the most severe dumping symptoms (Cases D1 and D2) showed grossly excessive jejunal peristalsis, by which the stomach, after being almost empty at three minutes, was partly filled and emptied again in rapid alternation. Moderate dilatation of the efferent loop of the jejunum was seen in six of the nine patients who had dumping attacks, in one of the eight patients who had hypoglycaemic attacks alone, and in none of the seven gastrectomy patients examined who were free of symptoms. Partial filling of the afferent loop was found in two of the nine patients who had dumping attacks, but in none of the others. Four of our patients with dumping attacks (D1, D2, D3, and D4) were conscious of 'churning' or 'rolling' of the stomach after meals, which suggested intestinal hyperactivity. The familiar liability of hypertonic fluids to cause severe attacks is noted later. The patient D2, after drinking 850 ml. of hypertonic sodium chloride, passed a very large quantity of fluid per rectum 45 minutes later. At the same interval after all meals he usually experienced an explosive attack of diarrhoea. The patient D6, 60 minutes after eating tomatoes, noticed the skins in his motion.

3. *Similar observations after drugs or operations which relieved dumping attacks.* (1) *Hexamethonium bromide.* Two patients (D2, D4), out of four who were given a controlled trial of hexamethonium bromide by injection before meals, gained considerable relief of symptoms; the same effect was found by Glazebrook and Welbourn (1952). Glucose-tolerance tests after similar injections showed a less steep initial rise of blood-sugar levels than had been found without hexamethonium (Table II). (2) *Operations.* Two patients had a second operation, in both cases with some relief of the attacks. In one (D3) a narrowing of the Polya-type stoma and the addition of a valve were followed by considerable relief of symptoms and an increase in weight and calorie intake. A more normal oral glucose-tolerance curve was found after the operation, and a more normal radiograph 10 minutes after a standard barium meal (Table II).

Summary (Table I). Patients subject to dumping attacks were characterized by small, very rapidly emptying stomachs, and intestinal hyperactivity, a differentiation which was made by oral glucose-tolerance tests, by 10-minute films after standard barium meals, and by 60- and 90-minute films after a barium-glucose mixture. The patients who had the most severe dumping

attacks also showed clearly excessive jejunal peristalsis after meals. Drugs and operations which relieved the attacks were found to diminish the rapidity of gastric emptying and the intestinal hyperactivity. Unusual filling of the afferent or efferent jejunal loops did not characterize the patients who had dumping attacks. In patients who were subject only to hypoglycaemic attacks the

TABLE II

Results of Oral Glucose-tolerance Tests before and after Hexamethonium Bromide or Operative Repairs in Three Gastrectomy Patients with Dumping Attacks

Patient	Blood-sugar (mg. per 100 ml.)														Absorption index (15+30+45-minute values in mg./100 ml.)
	0	15	30	45	60	75	90	105	120	135	150	165	180		
D2 Untreated	75	246	255	199	96	63	50	21	39	42	48	66	59	700	
After H.M.B.*	74	160	241	249	170	141	98	77	65	70	69	69	69	659	
D4 Untreated	74	171	230	234	220	183	134	86	59	50	40	52	58	635	
After H.M.B.*	78	114	153	172	157	160	150	120	83	60	61	60	61	439	
D3 Untreated	80	165	211	225	153	86	45	25	41	49	53	58	64	601	
After second operation†	87	158	183	196	219	225	182	129	103	79	61	63	75	537	

* After H.M.B.: test done half an hour after subcutaneous injection of 20 mg. hexamethonium bromide.

† After second operation; test done 14 days after narrowing of Polya-type gastric stoma with addition of valve.

stomach probably emptied no faster than in gastrectomy patients who had no symptoms.

II. Carbohydrate metabolism tests (Figs. 1 to 5)

In order to assess the basis of the liability of one group to post-prandial hypoglycaemic attacks, all groups were subjected, in addition to the oral glucose-tolerance test, to two tests which should give results independent of absorption, namely an intravenous glucose-tolerance test and an intravenous insulin-tolerance test. As in the oral glucose-tolerance test, the blood-sugar curves have been plotted as percentages of the fasting level, and the areas enclosed by the rise and the fall of these curves have been used as indices of the slopes of the curves, as shown in Figs. 2 and 3. Fig. 5 shows the correlation of the most significant measurement of this type, area A in the oral glucose-tolerance test, with the liability to dumping attacks. To elucidate the cause of the abnormalities revealed by the intravenous insulin tests, we made further metabolic studies of some of the patients liable to hypoglycaemia.

1. *The intravenous glucose-tolerance test* (Fig. 2) gave normal results in all groups.

2. *The intravenous insulin-tolerance test* (Fig. 3) showed delay in recovery from hypoglycaemia in all the groups of gastrectomy patients, implying a metabolic liability to hypoglycaemia. This delay was least in the symptom-free group (area $F = 19 \pm 3$, compared with the normal 9 ± 5) and in the group suffering from dumping attacks (area $F = 17 \pm 5$); it was obviously abnormal only in the group showing hypoglycaemic attacks (area $F = 29 \pm 7$) and in the two patients who were subject to both kinds of attack (area $F = 27$ and 38). Area F was above 25 in seven out of 10 of the patients who had hypoglycaemic

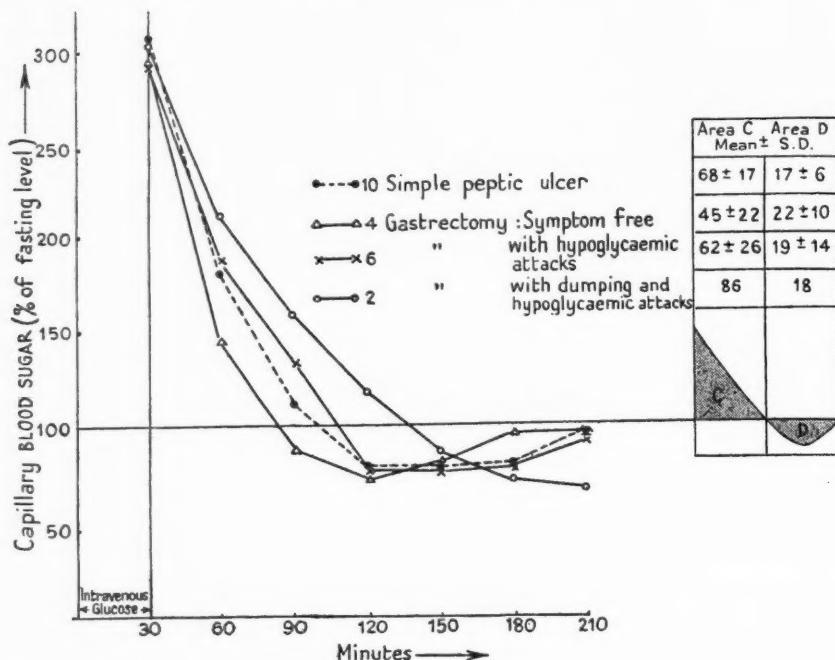


FIG. 2. Results of intravenous glucose-tolerance tests. The groups are not discernibly different by this test.

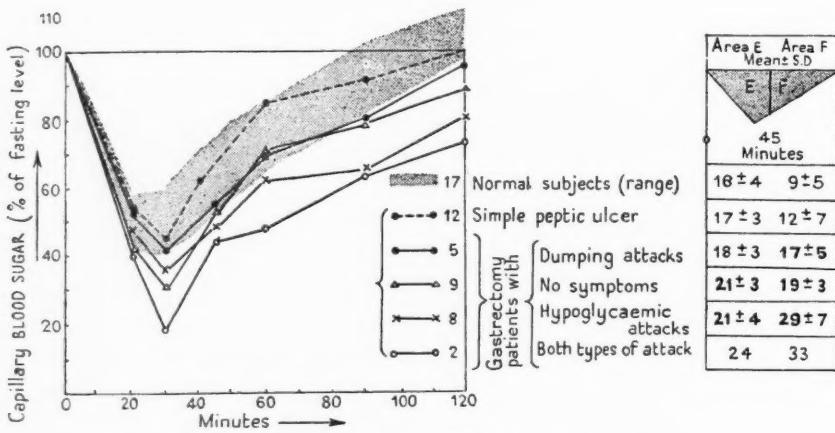


FIG. 3. Results of intravenous insulin-tolerance tests.

Note the delayed return from hypoglycaemia, best indexed by area F, found in both groups with hypoglycaemic attacks, and the similar but slighter defect in the other gastrectomy groups. This unresponsiveness to hypoglycaemia is probably due to reactive hyperinsulism. Figures in bold type are significantly different from the normal range.

attacks, and in no others; it was between 20 and 25 in the other three patients who had hypoglycaemic attacks, and in four out of 14 of the others. A simpler 'hypoglycaemic index' may be obtained from the sum of the blood-sugar values at 60, 90, and 120 minutes, low values in this case corresponding to high values of area *F*. Aggregate values of under 180 mg. per 100 ml. suggest a liability to hypoglycaemia, and were found in all hypoglycaemic patients but one, in one

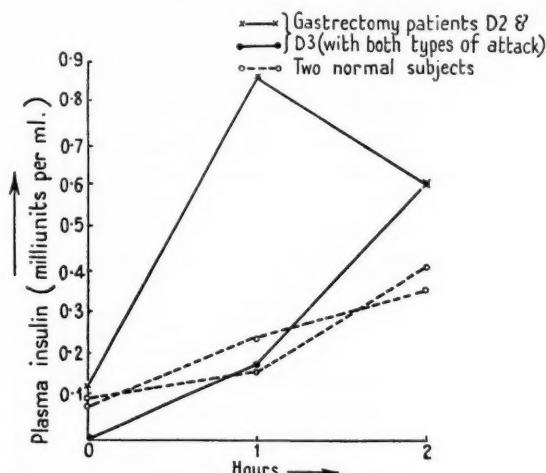


FIG. 4. Plasma-insulin assays during oral glucose-tolerance tests after a 12-hours' fast. Note the greater increase of plasma-insulin in the gastrectomy patients than in the normal subjects.

who had dumping attacks only, and in one gastrectomy patient who had no symptoms.

3. *The oral glucose-tolerance test* (Figs. 1 and 5), as already noticed, was mainly useful for revealing the rapid intestinal absorption consequent on rapid gastric emptying and intestinal hypermotility. Neither the rapid initial rise of the blood-sugar curve (area *A*) nor its final overswing into hypoglycaemia (area *B*) seemed to be specially characteristic of the group liable to hypoglycaemic attacks: this hypoglycaemic overswing (area *B*) was slightly increased among all groups. Hypoglycaemic symptoms at this phase of the test occurred in the two patients liable to both kinds of attack, in three of the other eight patients liable to hypoglycaemic attacks, in none of the seven liable to dumping attacks, and in one of the nine gastrectomy patients who were free of symptoms. Evidently only the more persistent overswings are likely to cause hypoglycaemic symptoms, and the degree of overswing is not a faithful reflection of the patient's liability to post-prandial hypoglycaemia. The insulin test was more suited to displaying a liability to hypoglycaemia, probably because of its greater and more consistent hypoglycaemic stress. Spontaneous attacks were usually encountered when ordinary meals were followed by exercise; such an association was noticed

by three of the 10 patients, while only one of them noticed their special likelihood after high-carbohydrate meals.

4. *Plasma-insulin assays* during oral glucose-tolerance tests (Fig. 4) were kindly made by Dr. J. Bornstein (Bornstein and Trewella, 1950) at 0, 1, and 2 hours after the standard glucose-tolerance test. In two patients who were subject to both dumping and hypoglycaemic attacks (Cases D2 and D3) the

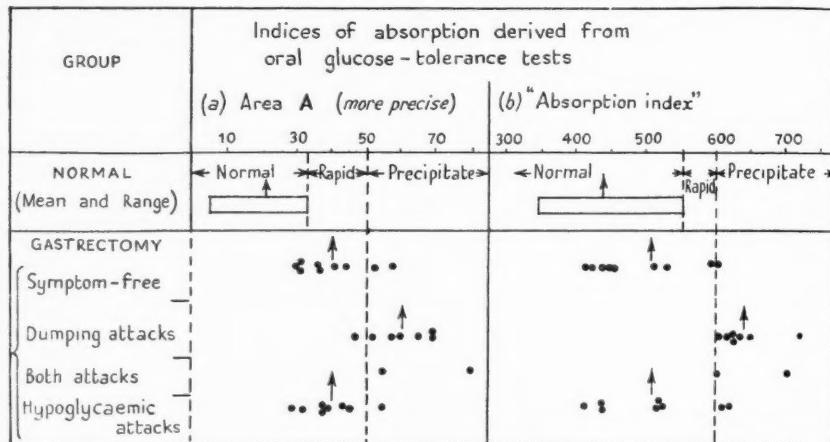


FIG. 5. Summary of the main findings from carbohydrate-tolerance tests.

The mean value for each group is shown by an arrow. Note the very rapid absorption, and therefore very rapid gastric emptying, in the group of patients with dumping attacks.

plasma-insulin levels rose excessively above normal fasting values, as compared with tests made on two normal subjects. Another patient, who had dumping attacks only (Case D1), showed a similar excessive rise. It thus appears that patients after gastrectomy may have functional hyperinsulinism.

5. *Further metabolic assessments* were made on two patients (Cases D2 and D3) who were liable to hypoglycaemic attacks. Normal anterior pituitary and adrenocortical function was indicated by normal 17-ketosteroid excretions (23.3 mg. and 18.7 mg. in 24 hours respectively) and Robinson-Power-Kepler tests of water diuresis; normal thyroid uptake was indicated in Case D3 by a radioiodine test.

Thus, by exclusion, it seems likely that the patients liable to hypoglycaemia have a functional hyperinsulinism which is greater than that of the other gastrectomy patients, and is presumably due to a greater reactivity to rapid gastric emptying and rapid absorption of sugar, since these factors in themselves were not greater in them than in gastrectomy patients who had no symptoms. That the patients subject to such attacks may have had a greater general nervous reactivity is suggested by the higher incidence among them of psycho-neurotic symptoms before operation (Table III).

Summary. 1. Patients liable to dumping attacks were usually distinguishable by a very rapid initial rise in blood-sugar on an oral glucose-tolerance test,

attributable to very rapid gastric emptying; in eight out of nine cases area *A* was over 50; or by the simpler 'absorption index', the sum of the 15-, 30-, and 45-minute blood-sugar values was over 600 mg. per 100 ml. in all nine patients.

2. Only the patients liable to hypoglycaemic attacks were characterized by an abnormal persistence of hypoglycaemia on the intravenous insulin-tolerance test; that is, their response to hypoglycaemia was defective. In seven out of 10 cases area *F* was over 25; or by the simpler 'hypoglycaemic index' the sum of blood-sugar values at 60, 90, and 120 minutes was under 180 mg. per 100 ml. in nine out of 10 cases. Tests of 17-ketosteroid excretion and water diuresis gave normal results in two of these patients, excluding adrenal cortical or anterior pituitary defect. This fact suggested that the basis of their attacks was hyperinsulinism, attributable possibly to their nervous over-reactivity.

3. All other gastrectomy patients showed the two preceding abnormalities in a lesser degree. They also showed a slightly increased hypoglycaemic overswing on the oral glucose-tolerance test; this was not characteristic of any group, and was only rarely associated with hypoglycaemic symptoms.

4. An abnormal increase of plasma-insulin after oral glucose was found in three gastrectomy patients, and, in view of the results of glucose- and insulin-tolerance tests, may be found in all such patients. Thus all patients who have undergone gastrectomy may have some functional hyperinsulinism, due probably to rapid absorption of sugar.

III. *The phenomena of the dumping attack*

Symptoms. A typical dumping attack began during a meal, or within 30 minutes of beginning one. The first symptoms were abdominal fullness and 'rolling' or 'churning' sensations, nausea and occasionally vomiting, palpitation or a sensation of 'pressure' about the head, dimness of vision, dizziness, faintness, heaviness of the eyes, 'hot and cold' feelings, dryness of the mouth, and, usually only in the earlier attacks, a feeling of apprehension. At the same time, or more usually 10 to 30 minutes later, complaint was made of weakness, fatigue, and drowsiness, and patients said they felt 'entirely useless' (Case D6), 'all in' (Case D4), 'completely exhausted' (Case D2) or 'limp and stupid and terribly drowsy' (Case D1). The phase of palpitation usually lasted 30 to 45 minutes; the weakness, fatigue, and drowsiness persisted in severe attacks for 90 to 180 minutes.

Indications of the release of a vasoconstrictor substance during the initial vaso-motor symptoms. (1) *Observations after the standard meal.* During the initial symptoms of palpitation, dizziness, 'hot and cold' feelings, and dryness of the mouth, the pulse-rate increased (mean rise 18 per minute) and the blood-pressure increased (mean rise 17/4 mm. Hg); sweating of the forehead and hyperpnoea were also noticed. Seven normal subjects after a similar meal showed a mean rise in the pulse-rate of 7 per minute, and in the blood-pressure of 4/0 mm. Hg. The normal post-prandial rise of temperature in the extremities (Booth and Strang, 1936) was delayed until after the dumping attack (Smith, 1951). During the attack the fingers of patients D2 and D3 became first pale and later

cyanotic. (2) *Comparable effects from infusions of adrenaline and other drugs.* Comparative observations were made on two patients during and after continuous intravenous infusions of adrenaline (0.17 mg. during half an hour in Case D2 and during one hour in Case D3), and of acetylcholine (1.5 gm. during 16 minutes in Case D2). The adrenaline reproduced an attack which was indistinguishable by the patients from the post-prandial attack, and which showed equivalent rises in pulse-rate and blood-pressure, with similar pallor and minor sweating. The electrocardiogram (limb lead 2) also showed the same changes as those seen in the dumping attack: in both patients there was a lowering of the T wave, and in patient D3 an exaggerated U wave and runs of nodal extrasystoles. But the post-prandial attacks were not influenced by moderate doses of the adrenergic-blocking drugs benzodioxane and dibenamine, which should have diminished endogenous adrenaline effects. On the other hand, Butler and Capper (1951) found that sympathetic block abolished the vasomotor symptoms of the dumping attack. During the acetylcholine infusion palpitations and 'hot feelings' were noticed, and there was a moderate increase in the pulse-rate, but the mouth remained moist, the face became flushed, and the patient's feelings were different from those noticed in his post-prandial attacks.

Evidence of potassium deficiency in the later phases of weakness. In a severe attack weakness, fatigue, and drowsiness followed the initial vasomotor symptoms, and were the most persistent features of the attack; indeed, some patients, for example Case D9, were aware of no vasomotor phase, but only of these symptoms. The following evidence, already presented elsewhere (Smith, 1951), indicates that this weakness may be due to potassium deficiency: (1) During the phase of weakness there is a greater fall in serum-potassium concentration than in symptom-free gastrectomy patients, usually of about 1 mEq. per litre, and reaching its trough at about 90 minutes after the meal. (2) There are concurrent electrocardiographic changes indicating potassium deficiency: flattening or inversion of the T wave, an exaggerated U wave, sagging of the ST segment, and an increase in the height of the P wave. Serial electromyographic records of the response to stimulation of the small muscles of the hand during the attack also indicated, at the same stage, an impairment of 13 per cent. and 20 per cent. in two patients; this finding is compatible with potassium deficiency, as well as confirming the weakness objectively. (3) Potassium given intravenously at this stage relieves the weakness, restores the electrocardiogram to normal, and terminates the attack prematurely. Infusions for 40 to 90 minutes, at rates of 0.8 to 2.4 mEq. potassium per minute, were given.

Summary. The symptoms and signs of the initial vasomotor phase of the attack suggest the release of a vasoconstrictor like adrenaline, but are not modified by adrenergic block; the weakness and drowsiness which follow are probably due to potassium deficiency.

IV. Some contributory and precipitating causes of the attacks

Precipitating factors observed to modify the dumping attacks. Of the nine patients who had dumping attacks, six noticed especially severe attacks after

bulky meals, five after sweet foods and drinks, three after milk, cheese, or eggs, and one after liquid meals. Ingestion of equal large volumes of fluid, whether hypertonic saline (2·7 per cent. NaCl), glucose (15 per cent.), or protein (6 per cent. calcium caseinate), caused severe attacks; slight attacks followed barium and water, and attacks which were slighter still followed water alone. With patient D2 it was observed that an attack began 10 to 13 minutes after beginning our standard breakfast, but after a similar volume of hypertonic glucose

TABLE III
Incidence of some Associated Disorders after Gastrectomy

<i>Associated disorder</i>	<i>Incidence among patients after gastrectomy</i>			
	<i>With dumping attacks</i>	<i>With both types of attack</i>	<i>With hypoglycaemic attacks</i>	<i>With no attacks</i>
Loss of weight over $\frac{1}{2}$ stone (mean loss)	6/6 (24 lb.)	2/2 (27½ lb.)	6/8 (17½ lb.)	7/9 (16 lb.)
Diarrhoea	2/7	2/2	0/8	0/9
Steatorrhoea (proved by fat balance)	1/4
Psychoneurotic symptoms:				
(a) before operation	1/7	1/2	3/8	2/9
(b) after operation	5/7	2/2	3/8	2/9
Bilious vomiting	2/7	2/2	0/8	0/9
Vitamin deficiency or anaemia	2/7	0/2	0	0

taken in the same sitting posture similar symptoms began in one and a half to three minutes.

Associated disorders after gastrectomy. Table III shows the incidence of other disorders found after gastrectomy in the three groups of patients. Among those liable to dumping attacks diarrhoea (usually without steatorrhoea), loss of weight, and concurrent psychoneurotic symptoms, were more frequent or more severe; these disorders may all be attributable to the intestinal effects of the dumping attacks. The only feature possibly more frequent among those liable to hypoglycaemic attacks was evidence of psychoneurotic disorder before operation; but with such small groups, and with retrospective psychiatric assessment, this is mentioned only as a suggestion.

V. Clinical trial of some medical treatments for dumping attacks

In treating four of the patients who had dumping attacks, controlled trials were made in hospital with various drugs, including appropriate 'dummy' tablets and injections; at frequent intervals the drugs were changed without the knowledge of either the patient or the assessor. Two patients, D2 and D3, obtained significant relief from a diet high in protein, low in carbohydrate, and with minimal fluid at meals. All patients knew that the attacks were less severe if they lay down. No relief greater than that obtained from inert tablets was derived from many oral drugs including banthine (an anticholinergic drug), dibenamine and benzodioxane (adrenergic blocking drugs), ephedrine, pentamethonium iodide, phenergan, and phenobarbitone. The vasomotor symptoms were little altered, but the weakness was cut short or eliminated, after potassium

chloride given orally, and more so when given intravenously, either before the meal or at the onset of the attack; this occurred in all three patients so treated. Two of four patients who were given hexamethonium bromide injections before meals gained the greatest relief that was obtained with any medical treatment; presumably it acted by diminishing the gastro-intestinal hurry. The dose used was 25 to 50 mg. half an hour before food, or the largest dose short of undesirable vasomotor side-effects. As already mentioned, and shown in Table II, this drug also diminished the very rapid initial rise in blood-sugar which was otherwise found on performing the oral glucose-tolerance test.

Discussion

Our findings offer evidence in support of Hertz's original (1913) theory of the primary dependence of dumping attacks on 'too rapid drainage of the stomach'. Our group of patients who had dumping attacks was distinguished from all our other gastrectomy groups by signs of precipitate gastric emptying disclosed both by X-ray and by oral glucose-tolerance tests. In our other gastrectomy patients gastric emptying, though rapid, was only rarely and never consistently in the same range of rapidity. The gastric emptying-rate to be expected after gastrectomy without dumping attacks has probably been adequately defined from the other two groups of patients, those chosen for their liability to hypoglycaemic attacks only, and those chosen as being symptom-free; in these two groups the range was found to be equivalent both by radiological and by oral glucose-tolerance tests. There are many reasons why this evidence should have hitherto proved elusive. It is notoriously difficult to find the gastric emptying-rate which is characteristic of an individual rather than of his circumstances during the test; even when posture and the volume and composition of the test meal are controlled, it is difficult to standardize the patient's nervous state during the test. Conventional procedures tend to overlook the differentiation required between rapid and very rapid emptying. In using the oral glucose-tolerance test a sensitive index of absorption must be based on blood samples taken at least every quarter of an hour for the first 45 minutes after a standardized volume of glucose solution. Further, our comparison was facilitated by being made between extreme groups of gastrectomy patients, those who were symptom-free and those who suffered from persistent and fairly severe dumping attacks. Nevertheless, though the group differences were significant, no single test completely segregated all patients who had dumping attacks, probably partly because of the difficulties in assessing gastric emptying, and partly because of individual variations in the degree of its rapidity sufficient to induce the attacks. But in view of the need for some objective index of the liability to dumping attacks, the methods used should have clinical value if the results are interpreted with proper judgement. Minor degrees of this disability would not be revealed by such methods, but the lesser attacks tend to remit spontaneously. Gastric emptying which is more rapid than that found among our gastrectomy patients who had no symptoms may be regarded as 'precipitate' or very rapid, and as indicating a liability to dumping attacks. Such a degree of rapidity is

shown by an empty stomach 10 minutes after a standard barium meal, or by an oral glucose-tolerance curve with an area A above 50 or with the sum of the 15-, 30-, and 45-minute blood-sugar values over 600 mg. per 100 ml. When the indices of gastric emptying do not at least closely approach this 'precipitate' range, disabling dumping attacks can probably be excluded. Such rapid gastric emptying may not be entirely attributable to the operation. As already mentioned, some patients who have dumping attacks may be predisposed before operation to develop rapid gastric emptying, intestinal hurry, and dumping attacks; but there is better evidence that the incidence of such attacks varies with the type of operation performed. When very rapid gastric emptying develops, it is likely that the type of operation has been inappropriate to the patient.

Most of the mechanisms involved in the dumping attack can be understood as consequences of precipitate gastric emptying. Many experiments with feeding by jejunostomy, or by a jejunal tube, have shown that typical dumping attacks follow excessive stimulation of the jejunal mucosa (Alvarez, 1949; Adlersberg and Hammerschlag, 1947) by the cold of iced water, by the mechanical effects of dilatation with a balloon, or the rapid entry of a large volume of isotonic fluid, or by the irritant effect of smaller volumes of hypertonic solutions of saline, glucose, or protein. Given very rapid gastric emptying, the factors which the patients find to cause severe attacks are those which would increase jejunal stimulation after meals; such factors are the erect posture, bulky meals, and liquid or sweet foods. Precisely how these stimuli lead to the syndrome of the attack is not yet fully clear. The premonitory minor symptom of abdominal fullness is presumably due to such jejunal stimulation and resulting hypermotility. Intestinal hypermotility after such stimuli, and also during the dumping attack, has been shown by radiology and kymography (Glazebrook and Welbourn, 1952). This hypermotility itself may further exaggerate the rapid gastric emptying; and when, in some patients, this vicious circle is diminished by hexamethonium bromide, the tests show slower gastric emptying, and the severity of the dumping attack is relieved. Within a few minutes of the abdominal fullness the attack proper begins with its vasomotor symptoms; these are associated with signs of a circulating vasoconstrictor, whose source and nature has not yet been defined. This syndrome is apparently reproduced by an adrenaline infusion, but it is not diminished by adrenergic block; Butler and Capper (1951) found that sympathetic block prevented this and the other systemic components of the attack, but did not further define the mechanism involved. Within a further 15 to 30 minutes the final phase of the attack follows, during which the vasomotor symptoms slowly subside. We have shown this final phase of weakness to be due to potassium deficiency, for it is associated with lowered serum-potassium and electrocardiographic and electromyographic evidence of such a deficiency, and is rapidly abolished by an infusion of potassium chloride. Two phenomena of the attack are together probably sufficient to account for potassium deficiency: rapid glycogen deposition consequent on the rapid absorption of glucose, and the release of an adrenaline-like

vasoconstrictor; for both glycogen deposition (Harrop and Benedict, 1922-3; Kendall, 1938) and adrenaline (Castleden, 1937-8; Hildes, Sherlock, and Walshe, 1948-9) are known to cause a fall in serum-potassium and free tissue potassium. Various other theories of the cause of dumping attacks were introduced before it was clear that very rapid gastric emptying characterized the patients who suffer from them. We have not found kinking or distension of the afferent jejunal loop characteristic of such patients. Drag on the lesser omentum seems an unlikely cause, and was not demonstrable in our patient who had had vagotomy. Mercury bags dropped into the stomach of such patients might readily enter the jejunum and cause attacks by irritating it.

Since the primary causes of dumping attacks are evidently rapid gastric emptying and consequent intestinal hypermotility, medical treatment should aim at diminishing these abnormalities and at improving the associated malnutrition which exacerbates them; but our search for measures adequate to relieve the severely affected patients has been disappointing. Dry meals rich in protein and poor in carbohydrate, supplementary vitamins, and lying down after meals, are helpful measures. Injection of hexamethonium bromide before the main meals gives considerable relief to some, but not to all patients; potassium salts, taken as table salt at meals, diminish the weakness but not the other symptoms. Small volumes of concentrated, or sufficiently large volumes of dilute potassium chloride themselves induced the symptoms. No other drug of the many which were tried helped the patients more than inert tablets. Persistence of frequent and severe attacks beyond six to 12 months, if associated with the signs of very rapid gastric emptying described above, probably justifies operative reconstruction of the gastrectomy, provided that the surgeon can offer a good prospect of mechanical improvement.

Our patients who had post-prandial hypoglycaemic attacks were distinguishable from the other gastrectomy patients by the intravenous insulin-tolerance test, which showed a slow return of the blood-sugar from the hypoglycaemic levels induced by insulin, a result comparable with Barnes's (1947) finding of insulin hypersensitivity. In this test an area F over 25, or a sum of the 60-, 90-, and 120-minute blood-sugar values which is less than 180 mg. per 100 ml., indicates a slow return from hypoglycaemia. Since these patients showed evidence neither of severe liver impairment nor of lack of insulin antagonists in the anterior pituitary and adrenocortical secretions, this finding was probably evidence of hyperinsulinism. The intravenous insulin-tolerance test showed the same defect, in a much slighter degree, in all our gastrectomy patients; in all these the defect may be attributed to rapid absorption of carbohydrate leading to an excessive insulin response. An excessive increase of plasma-insulin after oral glucose was found in the three gastrectomy patients to whom this test was applied. But the greater abnormality found in the patients who were liable to hypoglycaemic attacks must be due to a greater responsiveness to the same basic stimulus rather than to a greater stimulus, for after oral glucose these patients did not show a steeper rise in the blood-sugar curve than the other patients who had had gastrectomy, and other workers have observed similar results

(Evensen, 1942). The greater degree of post-prandial hyperinsulinism apparently present in our patients who had hypoglycaemic attacks may have been due to excessive nervous reactivity; there seems to have been a higher incidence among them of psychoneurosis before operation, as other observers have found in similar cases. Neurotic instability has also been found among certain patients who have had no operation but have been liable to similar post-prandial hypoglycaemic attacks (Wilder, 1940; Conn, 1940), and a liability to such hypoglycaemic attacks is found among patients who have peptic ulcer, without operation (Straaten and Hünermann, 1939; Edlén, 1950). Thus a liability to post-prandial hypoglycaemia, present before operation, is probably the main basis of these attacks, though the tendency has often remained subclinical until gastrectomy added its slight, and otherwise subclinical, predisposition to hyperinsulinism and hypoglycaemia. Fortunately the attacks are usually mild. Their treatment should therefore be directed to improving the nervous state and any malnutrition which would exacerbate it, as well as advising sufficiently frequent meals.

We wish to acknowledge our indebtedness to Dr. J. Bornstein for the plasma-insulin assays, and to many medical and surgical colleagues at Hammersmith Hospital for referring patients for study.

APPENDIX I

Details of Methods Used

1. *Standard barium meal.* Ten ounces (300 ml.) of standard barium-meal suspension were given orally to the patient in the erect posture, and a radiograph of the stomach was taken after 10 minutes.

2. *Barium-glucose meal.* A mixture of one part of standard barium-sulphate suspension added to four parts of 15 per cent. glucose solution (1 gm. per kg. body-weight) was taken orally by the patient in a standard sitting position. Radiographs were taken five minutes later, and half-hourly for three hours. The patient remained in the sitting position throughout the test, except when moving to and from the near-by X-ray machine.

3. *Carbohydrate metabolism tests.* Before all carbohydrate tests it was ascertained that the patient was free from recent infection. An adequate and steady dietary intake, including 250 to 400 gm. of carbohydrate per day, was ensured for at least four days prior to each test, and a 12-hour fast was required before each test. (1) *Oral glucose-tolerance test.* Glucose, 1 gm. per kg. of body-weight in 15 per cent. solution, was given to the patient in a standard sitting position. Duplicate samples of capillary blood were taken fasting and every 15 minutes for three hours. (2) *Intravenous glucose-tolerance test.* Glucose, 0·5 gm. per kg. body-weight in a 20 per cent. solution, was given intravenously over 30 minutes (Thorn, Koepf, Lewis, and Olsen, 1940). The blood samples were taken with the patient in a semi-recumbent position. (3) *Intravenous insulin-tolerance test.* Insulin, 0·1 unit per kg. body-weight, was given intravenously, and duplicate samples of capillary blood were taken fasting and at 20, 30, 45, 60, 90, and 120 minutes (Fraser, 1943). (4) *Blood-sugar* was estimated by the

titrimetric method for 'true sugar', Harding's modification of the Schaffer-Hartmann method (King, 1951).

4. The 'standard meal' used in studying the phenomena of the dumping attack has been described by Smith (1951).

APPENDIX II

Details of Gastrectomy Patients

<i>Case number (sex, and age in years)</i>	<i>Reason for gastric operation</i>	<i>Type of gastric operation</i>	<i>Time from operation to tests</i>	<i>Time of onset of attacks after meals</i>
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GROUP I. Patients with no symptoms

C1 (F, 40) 56558	Duodenal ulcer, 4 years	Polya partial gastrectomy	1 year	..
C2 (M, 38) 100016	Duodenal ulcer, 5 years	Polya partial gastrectomy	9 months	..
C3 (M, 60) 82661	Gastric ulcer, 2 years	Polya partial gastrectomy	1½ years	..
C4 (M, 43) 27518	Prepyloric ulcer, 11 years	Polya-Hofmeister partial gastrectomy	1¼ years	..
C5 (M, 35)	Duodenal ulcer, 14 years	Gastro-enterostomy and later vagotomy	1½ years	..
C6 (F, 42)	?Duodenal ulcer, 26 years	Billroth I partial gastrectomy	10 months	..
C7 (F, 42)	Gastric ulcer, 8 years	Billroth I partial gastrectomy	2 years and 10 months	..
C8 (M, 55) 14531	Gastric ulcer, 18 months	Polya partial gastrectomy	2 years and 2 months	..
C9 (M, 58) 85324	Adenocarcinoma of stomach	Polya subtotal gastrectomy	3 years and 4 months	..

GROUP II. Patients with dumping attacks

D1 (F, 49) 110733	Duodenal ulcer, 15 years	Polya partial gastrectomy	9 months	Immediate and after 15-30 min.
D4 (M, 58) 89492	Duodenal ulcer, 12 years	Polya partial gastrectomy	4 years	20-30 min.
D5 (M, 57) 83496	Thoracic stomach with short oeso- phagus	Total gastrectomy	15 months	10-20 min.
D6 (M, 47) 77106	?Duodenal ulcer, 6 years	Vagotomy	4 years	..
D7 (M, 57)	Duodenal ulcer, 10 years	Polya partial gastrectomy	2 years	Immediate
D8 (M, 39) 86007	Duodenal ulcer, 4 years	Polya partial gastrectomy	18 months	10-20 min.
D9 (M, 63)	Duodenal ulcer, 10 years	Polya-Hofmeister partial gastrectomy	16 months	10-20 min.

CAUSES OF POST-PRANDIAL ATTACKS OF PALPITATION 401

APPENDIX II (*contd.*)

Case numbers (sex and age in years)	Reason for gastric opera- tion	Type of gastric opera- tion	Time from operation to tests	Attacks		
				Time of onset after meals	Relief of attacks	Blood-sugar in late attack (mg./100 ml.)

GROUP III. *Patients subject to both attacks*

D2 (M, 45) 87381	Duodenal ulcer, 7 years	Billroth I partial gastrectomy and vagotomy, followed by gastroentero- stomy 1 week later	2 years and 8 months	10-15 min. and 1½ hrs.	Sweet drinks (late attacks)	38
D3 (M, 50) 16897	Duodenal ulcer, 8 years. One perforation	Polya partial gastrectomy	3½ years	15 min. and 2-3 hrs.	..	56

GROUP IV. *Patients with hypoglycaemic attacks*

H1 (M, 52) 32139	Duodenal ulcer, 20 years	Vagotomy	4 years	2-3 hrs.	Sweet tea	56
H2 (M, 63) 24588	Perforated duodenal ulcer	Billroth I partial gastrectomy
	Anastomotic ulcer	Vagotomy (23 years after gastrectomy)	3 years	1½-3 hrs.
H3 (M, 54) 117823	Gastric ulcer, 13 years	Polya partial gastrectomy	8 years	1½-2 hrs.	Carbo- hydrate food or sugar	..
H4 (M, 52) 49187	Duodenal ulcer, 12 years	Vagotomy and gastro- enterostomy	3 years 9 months	1½-2½ hrs.	Sugar	..
H5 (M, 27) 77073	Duodenal ulcer, 6 years	Vagotomy	..	1½-2 hrs. (after vagotomy, and also, less frequently, after gastrectomy)	Sugar	..
	Recurrence of symptoms	Polya partial gastrectomy (1 year after vagotomy)	4 years and 2 months
H6 (M, 57) 119035	Gastric ulcer, 2 years	Billroth I partial gastrectomy	6 years and 9 months	1-2 hrs.	Tea and toast or biscuits	..
H7 (M, 46) 94629	Pyloric ulcer, 12 years	Polya partial gastrectomy	11 months	1½ hrs.
H8 (M, 62) 91742	Duodenal ulcer, 20 years	Polya partial gastrectomy	1 year and 10 months	2 hrs.	Food	..

Patient with jejunostomy after total gastrectomy

J1 (F, 56) 43671	Persistent dysphagia following repair of diaphragmatic hernia	Total gastrectomy with partial oesophagectomy. Jejunostomy 1 year and 2 months later	1 year after jejunostomy
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Summary

1. Detailed studies have been made of 17 patients who suffered for at least nine months after gastric operations from attacks of palpitation and weakness; these attacks occurred after meals either early (dumping attacks, in seven patients) or late (hypoglycaemic attacks, in eight patients) or in both forms (in two patients). These patients have been compared with nine who were free from such symptoms after similar operations, and with one patient who had a jejunostomy.

2. Gastric emptying was rapid in all the gastrectomy patients, but precipitate only in those who had dumping attacks; precipitancy was evident in the results of oral glucose-tolerance tests from the very rapid increase of blood-sugar (the sum of the 15-, 30-, and 45-minute blood-sugar values being over 600 mg. per 100 ml.), and in standard barium-meal examinations by the stomach being empty in 10 minutes, or after a barium-glucose meal in 60 minutes. Intestinal hypermotility immediately after meals probably also characterized all the patients who had dumping attacks. Among the patients subject to hypoglycaemic attacks the gastric emptying-rate, judged by radiological evidence and by oral glucose-tolerance tests, was equivalent to that found among the gastrectomy patients who were free from symptoms.

3. (1) By the oral glucose-tolerance test all the gastrectomy patients showed a moderately rapid initial rise in blood-sugar and a slightly excessive hypoglycaemic overswing, which were rarely associated with hypoglycaemic symptoms; only the group with dumping attacks was distinguished by a very rapid initial rise in blood-sugar. (2) An excessive increase of plasma-insulin after oral glucose was found in three gastrectomy patients who were tested. (3) In intravenous insulin-tolerance tests the patients who were liable to hypoglycaemic attacks were distinguishable by an abnormal persistence of hypoglycaemia (the sum of the 60-, 90-, and 120-minute blood-sugar values being under 180 mg. per 100 ml.); all the other gastrectomy patients showed a similar but lesser defect. (4) In two of the patients who were liable to hypoglycaemic attacks, tests of anterior pituitary and adrenocortical function were normal; their liability to hypoglycaemia seems attributable to greater functional hyperinsulinism, possibly due to nervous over-reaction.

4. The early vasomotor symptoms of the dumping attacks are associated with signs suggesting the release of a vasoconstrictor like adrenaline, but are not modified by adrenergic block; the subsequent weakness and drowsiness are associated with signs of hypokalaemia, and can be abolished by giving potassium chloride.

5. Injections of hexamethonium bromide before meals considerably relieved the dumping attacks in two of four patients so treated.

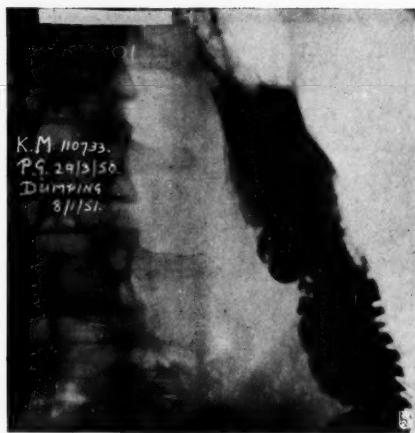
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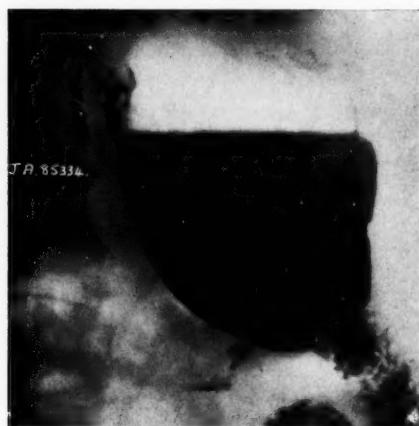
(a) Patient D2, liable to both types of attack



(b) Patient D1, liable to dumping attacks



(c) Patient C2, free from symptoms



(d) Patient C9, free from symptoms

FIG. 6 (a to h). X-ray picture 10 minutes after a standard barium meal in patients who have had gastrectomy. The stomach is empty in patients liable to dumping attacks (a, b, e, f), but not in those liable only to hypoglycaemic attacks (h) or free from symptoms (c, d, g)



(e) Patient D4, liable to dumping attacks



(f) Patient D3, liable to both types of attack



(g) Patient C8, free from symptoms



(h) Patient H8, liable to hypoglycaemic attacks

FIG. 6 (a to h). X-ray picture 10 minutes after a standard barium meal in patients who have had gastrectomy. The stomach is empty in patients liable to dumping attacks (a, b, e, f), but not in those liable only to hypoglycaemic attacks (h) or free from symptoms (c, d, g)

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THE EFFECTS OF GENERAL ANAESTHESIA, AND HEXAMETHONIUM, ON THE BLOOD-SUGAR IN NON-DIABETIC AND DIABETIC SURGICAL PATIENTS¹

By J. A. GRIFFITHS

(From the Royal Infirmary Unit, United Sheffield Hospitals)

RECOMMENDATIONS regarding the preparation of diabetic patients for operation vary considerably, as Rolland (1952) has recently observed. The common practice among anaesthetists and physicians now seems to be the giving of a carbohydrate feed, usually glucose in milk or lemonade, or where oral feeding is contra-indicated intravenous glucose solution, together with an injection of soluble insulin, in the period immediately before operation (Graham, 1945; Hewer, 1944a; Lawrence, 1950). Galley (1949) followed common usage in stipulating that all patients taking protamine-zinc insulin should be restabilized on morning and evening doses of soluble insulin, except in emergency cases. Hewer (1944a) recommended omitting the usual meal, and substituting 50 gm. of glucose, while Graham (1945) preferred to give 50 gm. of glucose in addition to the meal or its carbohydrate equivalent. Some authorities recommend a fixed dose of insulin, but Evans (1949) advocated that the dose should be adjusted to the previous diet, the degree of control, and the proposed anaesthetic agents. In the author's experience of 108 controlled diabetic patients prepared for anaesthesia in the latter way, only two cases have given rise to any anxiety. In these cases, described below, hypoglycaemia occurred towards the end of the operation, in which the technique of controlled hypotension for the reduction of blood-loss was used (Enderby and Pelmore, 1951).

Case Reports

Case 1. A woman aged 42 years had carcinoma of the right breast, and underwent radical mastectomy. She had had no previous anaesthetic. She was known to have had diabetes for 18 years and was treated by diet (16 black and 10 red Lawrence lines) and insulin (30 units protamine zinc and 15 units soluble each morning) for 16 years. Her weight was 63.5 kg. The cardiovascular, respiratory, and central nervous systems were normal, the blood-pressure 130/78, and the retinae normal. Reports of urine tests were '6 a.m. "green", 12 midday "green", 6 p.m. "red"; no other abnormality'. The haemoglobin was 14.5 gm. per 100 ml. *Pre-anaesthetic preparation.* The insulin was changed for seven days to 26 units soluble in the morning and 20 units soluble in the evening. The operation was timed for 2 p.m. She had the usual breakfast, with 20 units of soluble insulin, and a mid-morning drink at 10.30 a.m., and was given 40 gm. glucose in 200 ml. of milk and 12 units of soluble insulin at 11 a.m. Papaveretum 20 mg. and scopolamine 0.43 mg. were given subcutaneously at 12.30 p.m.

¹ Received January 30, 1953.

Anaesthetic. Induction was by 5 per cent. thiopentone sodium (0.45 gm.), and gallamine triethiodide 80 mg. Inflation with oxygen was followed by oro-tracheal intubation with a plain No. 9 Magill tube; a moist oral pack was inserted. Maintenance was with nitrous-oxide:oxygen (60:40 per cent.) on the semi-closed circuit with carbon-dioxide absorption. Intravenous pethidine (total dose 40 mg.) was employed as a supplement.

The blood-pressure after induction was 126/72, and the pulse-rate 70. Five minutes later, after a 30° foot-down tilt, the blood-pressure was 115/68, and pulse-rate 74. Fifty mg. of hexamethonium bromide were given intravenously, and within five minutes the blood-pressure was stabilized at 70/40, the pulse-rate being 82. The operation lasted 50 minutes; the reduction in blood-loss was most satisfactory, only nine swabs being stained. By the 40th minute a regular tachycardia of 108 per minute had set in, and at this stage the patient began to sweat profusely, and became pale and rather cold. Pure oxygen was given, and the patient was levelled; the blood-pressure was now 86/44. A few minutes later there was no change. A clinical diagnosis of hypoglycaemia was made, but unfortunately a blood sample was not obtained for confirmation. Fifty per cent. glucose was administered intravenously. After 30 ml. had been given the pulse-rate had fallen to 88, and the patient was warmer, with more colour. After a further 20 ml. the pulse-rate was 84, the blood-pressure 88/42, and the face was pink, warm, and much drier. At the end of the operation a further 10 ml. of solution were given, and the patient reacted to extubation and opened her eyes. At 6.30 p.m. the blood-pressure had returned to 118/68, and the patient was taking fluids by mouth. The first specimen of urine was obtained at 2 a.m., and showed: 'Sugar: orange; acetone: a trace'. The blood-sugar was estimated at 7.30 a.m., and was 385 mg. per 100 ml. Urine analysis at 8 a.m. showed 'Sugar: orange; acetone: positive'. The institution of a four-hourly régime restored the blood-sugar to normal and abolished the acetonuria within 24 hours. The subsequent course was uneventful.

Case 2. A man aged 47 years had excision of a mixed salivary tumour of the right parotid. He had had no previous anaesthetic. He was known to have had diabetes for 15 years, treated by diet (18 black and 10 red Lawrence lines) and insulin (protamine zinc 30 units and soluble 20 units each morning). His weight was 62 kg. Clinical examination revealed no abnormality; the blood-pressure was 140/86. The retinæ showed slight narrowing of the arteries. Reports of urine tests were '6 a.m. "green", 12 midday "green", 6 p.m. "green" to "red"; no other abnormality'. *Pre-anæsthetic preparation.* The insulin was changed for six days to 28 units soluble in the morning and 22 units soluble in the evening. The operation was timed for 2.30 p.m. He received the usual breakfast and 20 units of soluble insulin, and a mid-morning drink. At 11.30 a.m. he received 50 gm. of glucose in lemonade and 20 units of soluble insulin. Papaveretum 20 mg. and scopolamine 0.43 mg. were given subcutaneously at 1.15 p.m. *Anaesthetic.* Induction was by 5 per cent. thiopentone sodium (0.5 gm.), and gallamine 100 mg. Inflation with oxygen was followed by oro-tracheal intubation with a plain No. 10 Magill tube. A moist oral pack was inserted. Anaesthesia was maintained with nitrous-oxide:oxygen (60:40 per cent.) on the semi-closed circuit with carbon-dioxide circle absorption. Intravenous pethidine (total dose 20 mg.) was used as a supplement.

The blood-pressure after induction was 118/76; after a 30° foot-down tilt it was 114/70. The blood-pressure fell to 68/38 after 40 mg. hexamethonium bromide given intravenously; the pulse-rate was 82. A very satisfactory dry field was produced for the operation, which lasted 40 minutes. There was no reaction

to extubation, and the patient remained unconscious; he was rather pale, quite dry, and warm, but there was a tachycardia of 126 per minute. A clinical diagnosis of hypoglycaemia was made, and was subsequently confirmed by estimation of the venous blood-sugar, which at this time was 37 mg. per 100 ml. Administration of 50 per cent. glucose solution was begun. After 35 ml. the patient swallowed, and moved his arms and hands. After a further 10 ml. he rejected his oropharyngeal airway and coughed; two minutes later he opened his eyes. At this stage the blood-pressure was 85/50, and the pulse-rate 88. Ten ml. of glucose solution were given intravenously 20 minutes later. Two hours after the operation the patient was taking fluids by mouth. Analysis of a specimen of urine passed three and a half hours after operation showed 'Sugar: red', and a specimen six and a half hours after operation showed 'Sugar: orange'. The blood-pressure was then 112/65. Two hours later the blood-pressure had returned to the level found before operation. Thirty gm. of glucose and 10 units of soluble insulin were given at this time. On the following morning urine analysis showed: 'Sugar: orange; acetone: faint positive', and the blood-sugar estimated at this time was 405 mg. per 100 ml. A six-hourly régime was instituted. The acetonuria disappeared within 24 hours, and further recovery was uneventful. An electrocardiogram performed on the fifth day after operation showed no abnormality.

These two cases suggested that intravenous hexamethonium bromide given to the patient under general anaesthesia, in a dose sufficient to produce profound hypotension, might also potentiate the action of parenteral insulin. Accordingly experiments were designed to investigate the effect of the anaesthetic technique, with and without hypotension induced with hexamethonium, on the general level of the blood-sugar in normal and diabetic subjects. In addition attempts were made to investigate the effect of hexamethonium on the response to insulin in two normal subjects.

Methods

Patients between the ages of 20 and 50 years, with a fasting blood-sugar of between 75 and 95 mg. per 100 ml., and a normal urine shown by testing three successive specimens, were selected. Only patients who had been taking a normal full diet for the preceding three months were included. All received 50 gm. of glucose by mouth three and a half hours, and papaveretum-scopolamine subcutaneously one and a half hours, before induction. Venous blood from the antecubital fossa was used for the blood-sugar determinations, being immediately placed in calcium fluoride tubes after withdrawal. Subsequently, and in no case more than three hours later, the sugar-content was estimated by the method of Fujita and Iwatake (1931). The anaesthetic technique consisted of induction with 5 per cent. thiopentone sodium and gallamine triethiodide given intravenously, inflation with oxygen, and oro-tracheal intubation with the largest size of tube which could be passed with ease. Maintenance was by nitrous-oxide:oxygen (60:40 per cent.) on the semi-closed circuit with carbon-dioxide circle absorption, supplemented by intravenous pethidine, and further doses of gallamine when required. Respiration was assisted when necessary, to ensure that full oxygenation was maintained at all times. The blood-pressure was determined by auscultation and a sphygmomanometer on the arm. When

the hypotensive technique was employed, the initial dose of hexamethonium bromide was based on the response of the blood-pressure to the induction agents and to the adoption of a foot-down tilt. Specimens of blood were taken five minutes before induction, five, 10, 20, 40, 60, 80, 100, and 120 minutes after completing the induction, and two hours after the end of the operation. Hexamethonium, when used, was given just after the five-minute post-induction sample

TABLE I
Twenty Non-diabetic Subjects Undergoing Superficial Operations

All the patients were between 20 and 50 years of age, with a fasting blood-sugar between 75 mg. and 95 mg. per 100 ml., and analysis of three successive specimens of urine was normal. All received 50 gm. of glucose by mouth 3½ hours, and papaveretum 20 mg. and scopolamine 0.43 mg. subcutaneously 1½ hours, before induction, and the technique of anaesthesia was the same in each case.

Blood-sugar (mg./100 ml.)

Case number	Operation	Fasting	5 min. before induction				5 min. after induction				2 hrs. after operation				Extremes of blood-pressure							
			5	min.	before	induction	10	"	20	"	40	"	60	"	80	"	100	"	120	"	Highest	Lowest
3	Dissection, glands of neck	78	86	80	82	78	84	82	82	88	132/76	124/72
4	Left radical mastectomy	92	90	92	90	87	93	90	94	128/80	118/76
5	Excision, thyroglossal cyst	80	90	87	91	90	88	93	130/80	124/76
6	Tendon graft, right hand	92	92	80	84	85	82	83	84	82	86	142/84	122/74
7	Right radical mastectomy	75	84	88	86	93	95	92	90	132/88	118/74
8	Bilateral Trendelenburg and multiple ligations	84	86	81	85	88	84	85	82	83	84	82	82	122/68	116/70
9	Excision, left bronchial cyst	95	92	98	102	100	104	100	98	114/66	110/66
10	Bone graft, right tibia	88	84	85	82	85	86	84	83	87	138/86	122/78
11	Excision, right parotid	90	96	97	94	98	95	95	92	124/72	116/70
12	Skin graft, right leg	78	80	82	85	80	78	81	80	86	146/88	126/80
13	Tendon graft, left hand	86	95	92	88	92	90	94	88	90	92	94	138/70	128/68
14	Left Trendelenburg and multiple ligations	90	86	88	94	90	91	89	93	90	86	122/68	114/70
15	Right radical mastectomy	88	91	93	90	91	88	87	92	138/82	120/76
16	Bone graft, left radius	90	84	86	90	88	92	88	89	80	142/78	130/72
17	Bilateral Trendelenburg and multiple ligations	78	84	82	80	85	83	85	81	85	84	87	87	122/64	120/66
18	Bone graft, right tibia	76	87	89	86	85	88	86	90	144/88	130/80
19	Skin graft, left hip	92	87	88	92	94	90	91	86	136/80	124/72
20	Tendon graft, left hand	86	95	97	96	93	92	96	95	92	91	122/76	116/70
21	Dissection, glands of neck	76	81	87	82	80	78	82	82	83	86	128/70	120/68
22	Rotation flap, neck	84	92	95	98	95	96	94	90	122/72	114/66
	Mean	.	84.9	88.1	88.4	88.9	88.9	88.9	88.6	85.7	86.4	86.7	88.9									

was taken, and the operation was begun just before the 10-minute post-induction sample. Two non-diabetic patients each underwent three operations. In all three operations the standard anaesthetic technique was used. For the first operation each patient was prepared as above; for the second operation 15 units of soluble insulin were given subcutaneously one hour before induction; for the third operation soluble insulin was given similarly, and hypotension was induced with hexamethonium. Four controlled and well-prepared diabetic patients were studied. Three of these patients received the standard anaesthetic sequence; the fourth received hexamethonium.

Results

The results of the series of investigations in non-diabetic subjects are presented in three Tables. Table I shows 20 non-diabetic subjects submitted to operations involving only the body-wall or skeleton; Table II shows 10 non-diabetic subjects who underwent partial gastrectomy; Table III shows 25 non-diabetic subjects in whom the surgical procedure was limited to superficial

TABLE II
Ten Non-diabetic Subjects Undergoing Partial Gastrectomy

Selection, preparation, and anaesthesia as in Table I.

Blood-sugar in (mg./100 ml.)

Case number	Operation	Fasting	5 min. before induction				5 min. after induction				2 hrs. after operation				Extremes of blood-pressure		
			10	20	60	80	100	120	140	160	180	200	220	240	Highest	Lowest	
23	Partial gastrectomy	84	88	96	94	90	92	95	90	88	92	90	94	94	130/74	122/68	
24	"	85	92	96	90	88	94	90	95	92	88	90	90	90	126/72	108/64	
25	"	78	82	86	92	96	94	90	96	91	94	90	90	90	138/82	120/70	
26	"	82	80	78	85	82	84	84	80	82	85	84	84	84	136/72	122/64	
27	"	94	90	94	96	98	95	92	95	92	94	90	90	90	126/84	116/70	
28	"	82	90	92	98	95	94	98	93	96	94	92	92	92	120/72	112/66	
29	"	84	82	88	92	90	91	86	92	89	92	88	88	88	132/88	120/68	
30	"	82	94	106	112	114	110	116	112	114	114	114	128/78	120/66	
31	"	76	82	83	86	85	88	84	86	89	86	84	84	84	138/80	118/68	
32	"	95	91	98	100	97	102	100	104	102	102	102	132/76	126/66	
Mean		84.2	87.1	91.7	94.5	93.5	94.6	93.2	94.5	90.7	90.4	92.8					

structures, and in whom the technique of induced hypotension was used. The mean blood-sugar values for each period of observation, which are shown at the foot of each Table, were plotted against the time of the observation (Fig. 1). There is an unchanged mean level of blood-sugar in patients shown in Table I, a maintained rise in those shown in Table II, and a lowered blood-sugar in those shown in Table III. Such changes are significant, as is shown by the following statistical analysis. In all cases the operation was begun between the fifth and tenth minute after induction, and in the series with induced hypotension the fall in blood-pressure was induced before the start of the operation, in the same period. As the effects of the operation and of the induced hypotension appeared immediately after this period, and as such changes were maintained until the end of the operation, each series was divided into two groups for the purpose of statistical comparison. Thus for each of the series there were two groups of observations: one, the 'pre-surgical', which contained the observations made up to and including the fifth minute after induction of anaesthesia, and the other, the 'post-surgical', which contained the rest of the observations, from the tenth minute after induction of anaesthesia to the end of the operation. There are thus six groups in all, and the mean blood-sugar values in these groups are shown in Table IV. An analysis of variance (Table V) showed that there was an overall significant difference between the groups ($P < 0.1$ per cent.). The

best estimate of the standard error from these results is that obtained from the overall analysis, that is, the 'within group' variance. This variance could

TABLE III

Twenty-five Non-diabetic Subjects Undergoing Superficial Operations with Controlled Hypotension by Intravenous Hexamethonium Bromide

Selection, preparation, and anaesthesia as in Table I.

Case number	Operation	Blood-sugar (mg./100 ml.)												Extremes of blood-pressure		Blood-pressure 2 hrs. after operation
		Fasting	5 min. before induction	5 min. after induction	20 "	40 "	60 "	80 "	100 "	120 "	140 "	160 "	Highest	Lowest		
33	Excision, right parotid	82	86	82	76	72	74	148/88	72/38	96/52	
34	Left radical mastectomy	80	78	80	69	71	68	72	73	152/90	66/?	90/40		
35	Pedicle graft	75	76	78	82	80	83	80	116/68	98/58	118/66	
36	Right radical mastectomy	78	85	86	79	81	83	81	136/78	72/36	106/58	
37	Dissection, glands of neck	85	80	78	68	62	65	64	61	65	160/90	70/40	94/52	
38	Plastic repair, left ear	76	88	85	94	93	90	94	90	93	120/72	105/65	118/68	
39	Excision, left parotid	80	84	81	76	74	73	76	75	138/80	68/?	88/40		
40	Dissection, glands of neck	86	88	86	80	76	79	80	77	84	156/88	75/36	98/58	
41	Excision, thyroglossal cyst	95	91	87	79	76	79	75	77	..	120/68	70/?	90/48	
42	Left radical mastectomy	80	76	78	70	69	68	72	..	132/72	65/?	86/56	
43	Excision, left submandibular gland	..	86	96	93	95	97	94	95	126/68	90/50	104/56	
44	Excision, right parotid	..	82	92	90	81	83	80	94	128/80	72/38	110/62	
45	Rotation flap	..	76	79	81	69	72	70	70	75	132/68	68/?	92/48	
46	Excision, rodent ulcer of scalp	..	92	98	97	90	94	91	93	94	99	..	122/68	86/54	114/70	
47	Right radical mastectomy	78	82	80	73	69	66	71	78	142/78	70/?	94/40		
48	Dissection, glands of neck	91	90	91	84	80	78	82	80	162/92	72/34	98/56		
49	Right local mastectomy	79	75	71	62	58	61	64	126/74	65/?	86/36		
50	Left radical mastectomy	81	86	82	85	87	85	88	118/68	86/52	110/66		
51	Excision, left submandibular gland	..	80	84	86	73	76	75	80	120/68	70/36	102/50	
52	Excision, right bronchial cyst	75	78	82	80	79	82	81	84	116/68	74/32	106/54		
53	Right radical mastectomy	78	85	86	74	71	72	72	76	128/78	68/?	90/38		
54	Rotation flap, scalp	..	83	81	82	76	77	75	79	76	80	136/70	70/34	102/56		
55	Excision, right mandible	84	90	87	80	75	74	74	72	142/86	66/?	86/40		
56	Right radical mastectomy	88	92	94	86	82	83	90	136/80	70/36	100/48		
57	Excision, rodent ulcer of face	78	83	85	76	73	74	75	78	156/88	68/?	92/42		
Mean		..	81.9	84.9	84.3	78.3	77.1	77	77.6	79.6	80.7	

therefore be used to compare the differences between the mean levels of any pair of groups. These comparisons show that:

- In the series of 20 patients undergoing superficial operations there was no significant difference between the 'pre-surgical' and 'post-surgical' blood-sugar values ($P \geq 5$ per cent.).
- In the 10 patients submitted to partial gastrectomy there was a significant increase (2 per cent. $> P < 5$ per cent.) in the 'post-surgical' as compared with the 'pre-surgical' blood-sugar values.
- In the 25 cases in which the technique of induced hypotension was employed there was a significant fall ($P < 0.1$ per cent.) in the blood-sugar levels.
- There is a significant difference between the pre-surgical blood-sugar levels shown in Tables II and III, but not between the pre-surgical levels shown in Tables I and II, or in Tables I and III.

It can be seen from an inspection of Table III that the patients who showed little or no fall in blood-pressure in response to the injection of hexamethonium showed a similar lack of response in the blood-sugar (Cases 35, 38, 43, 50). From the same Table it appears that patients whose blood-pressure two hours

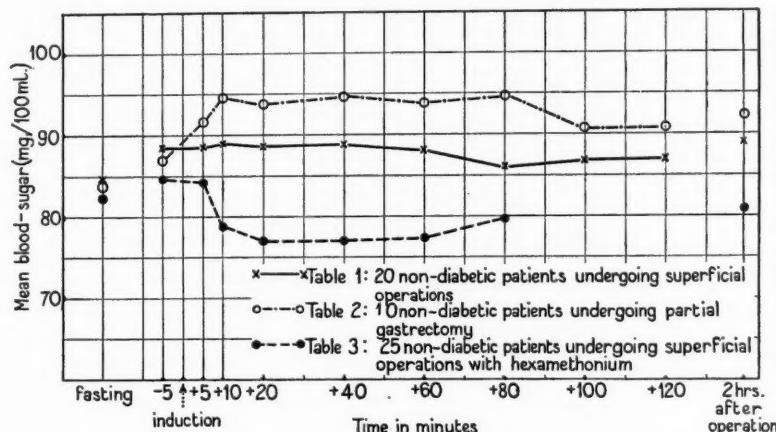


FIG. 1. Mean blood-sugar values in three groups of patients, showing (1) the steady level of blood-sugar in superficial operations; (2) the significant, but clinically unimportant, increase of blood-sugar in partial gastrectomies; (3) lowering of the blood-sugar level after administration of hexamethonium to induce hypotension.

TABLE IV

Mean Blood-Sugar Levels (mg./100 ml.) in 'Pre-surgical' and 'Post-surgical' Groups from Tables I, II, and III (Non-diabetic Subjects)

<i>From Table I (20 superficial operations)</i>		<i>From Table II (10 partial gastrectomies)</i>		<i>From Table III (25 superficial operations with hexamethonium)</i>	
'Pre- surgical'	'Post- surgical'	'Pre- surgical'	'Post- surgical'	'Pre- surgical'	'Post- surgical'
88.2	88.3	89.4	93.2	84.6	77.5

TABLE V

Variance Analysis derived from Table IV

<i>Source of variation</i>	<i>Degrees of freedom</i>	<i>Variance</i>	<i>Variance ratio</i>
'Between groups'	5	2,267	
'Within groups'	366	47.6	47.6
Total	371		

after operation had approached the pre-operation level also showed a restoration of the blood-sugar to pre-induction values (Cases 36, 44, 46, 52, 54, 56).

The blood-sugar values in two patients, each undergoing three superficial operations, are shown in Figs. 2 (Case 62) and 3 (Case 63). These figures clearly show the action of intravenous hexamethonium in potentiating the action of

parenteral insulin in the non-diabetic anaesthetized patient. It is to be noted that the decision to give intravenous glucose in Case 62 (Fig. 2) was based on the progressively increasing tachycardia beginning at the 45th minute and the onset of slight sweating at the 53rd minute, becoming profuse at the 58th minute,

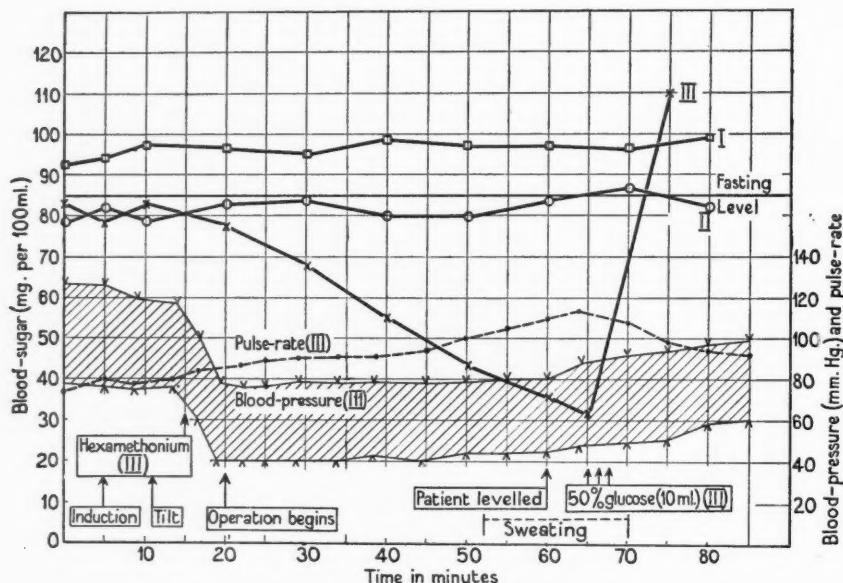


FIG. 2. Blood-sugar during three operations on a non-diabetic patient, showing potentiation of parenteral insulin by hexamethonium in the third.

Case 62. A man aged 38 years. No abnormality on clinical examination; blood-pressure 132/76; urine analysis normal. Operations I, II, and III, skin-grafting. The patient received 50 gm. of glucose in lemonade 3½ hours, and papaveretum 20 mg. and scopolamine 0.43 mg. 1½ hours, before each operation. All operations started 15 minutes after the induction of anaesthesia. One hour before operation II 15 units of soluble insulin were given subcutaneously; before operation III the same dose was given, but hypotension was induced with 60 mg. of intravenous hexamethonium bromide. Note in operation III the progressive tachycardia, and the onset of sweating at the 53rd minute, becoming profuse at the 58th minute, which were the only signs of the severe hypoglycaemia.

since the blood-sugar values for the 40th to 60th minutes had not then been estimated. In Case 63 (Fig. 3) similar considerations apply, but in this patient there was no sweating. It can be seen that relief of the tachycardia soon followed the intravenous administration of glucose in both cases.

The results in four patients with controlled diabetes are presented graphically in Fig. 4. All underwent superficial surgical procedures, and Case 61 received induced hypotension. All had been restabilized on morning and evening doses of soluble insulin, and all received their usual breakfast and morning insulin, and mid-morning drink, on the day of the operation. Glucose and soluble insulin were given one and a half hours before induction as follows:

<i>Case number</i>	<i>Glucose (gm.)</i>	<i>Soluble insulin (units)</i>
58	50	15
59	40	10
60	50	20
61	50	5

Cases 58, 59, and 60 showed a stable blood-sugar throughout the anaesthetic. Case 61 showed a precipitous decline in blood-sugar, and a progressive tachy-

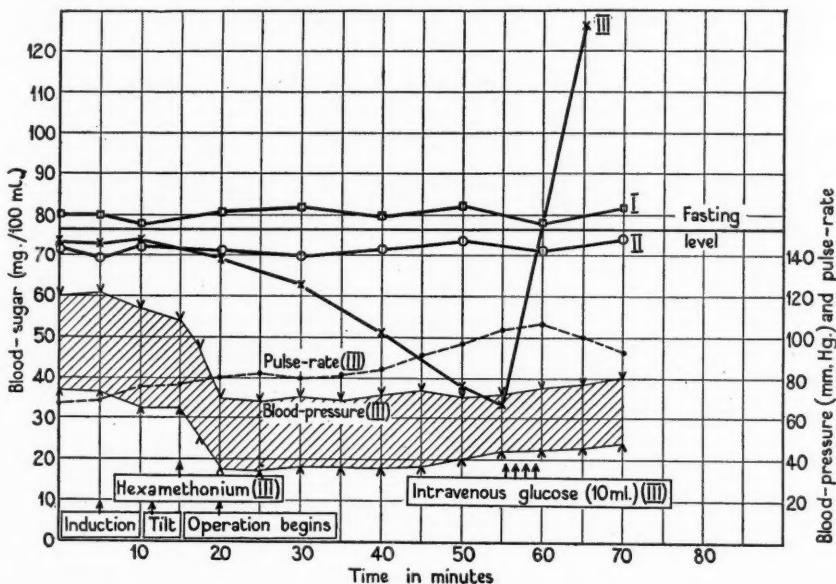


FIG. 3. Blood-sugar during three operations on a non-diabetic patient, showing potentiation of parenteral insulin by hexamethonium in the third.

Case 63. A man aged 45 years. No abnormality on clinical examination; blood-pressure 144/82; urine analysis normal. Operations I, II, and III, skin-grafting. Preparation as in Case 62 (Fig. 2). In operation III hypotension was induced with 40 mg. of hexamethonium bromide. Note the progressive tachycardia which was the only sign of hypoglycaemia in this case.

cardia after the 20th minute. At the 38th minute after induction of anaesthesia the pulse-rate was 116, and at this stage intravenous glucose was given, immediately after the 40th-minute blood-sample had been taken. Intermittent injections of 20 per cent. glucose were continued for three hours after the operation. There was no sweating or pallor in this case.

Discussion

Many anaesthetic agents produce some degree of hyperglycaemia, and Harris (1951) maintained that an increase of blood-sugar invariably occurs during all forms of anaesthesia, whether inhalation or intravenous, after hypnotics given orally or parenterally, and during local anaesthetic administrations by infiltration or by regional or spinal nerve block. An increase of blood-sugar follows

rectal bromethol or paraldehyde. Of inhalation agents chloroform is the most active in producing hyperglycaemia, followed by diethyl ether (Hewer, 1944a); methyl-*n*-propyl ether is as active as diethyl ether (Hunter, 1950), while divinyl ether is somewhat less active (Goldman, 1937). Trichlorethylene has an action less strong than diethyl ether (Haworth and Duff, 1943); cyclopropane

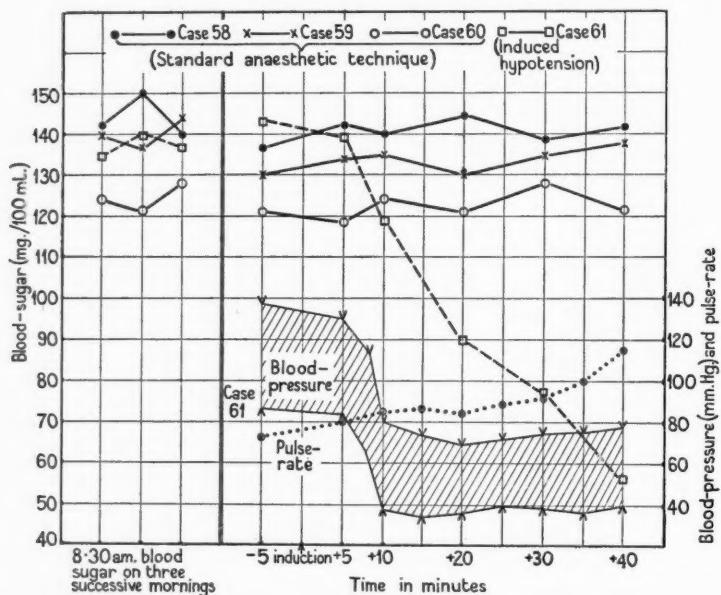


FIG. 4. Blood-sugar values in four patients with controlled diabetes during general anaesthesia for superficial operations, showing the striking fall in the blood-sugar level in the patient (Case 61) who received hexamethonium. The only sign of this degree of hypoglycaemia was the progressive tachycardia.

usually has only a slight effect (Pratt, 1938). Nitrous oxide, however, produces little or no effect on the blood-sugar (Adriani, 1942), and the same is true of intravenous single-dose thiopentone (Hewer, 1944b). It must be emphasized that such results with nitrous oxide and thiopentone depend on the maintenance of full oxygenation, as any degree of hypoxia rapidly produces *per se* a sustained hyperglycaemia due to sympatho-adrenal stimulation.

The increased blood-sugar content is derived from hepatic glycogenolysis (Harris, 1951), and seems to depend on two factors. The first is the direct action of a hepatotoxin (the anaesthetic agent) on liver-cells; this effect will depend upon the agent, the duration of administration, the concentration of the agent in the blood-stream, and the existing state of the liver. The second factor is sympathetic stimulation acting through the sympatho-adrenal mechanism; thus inadequate pre-medication in an apprehensive patient, or a troublesome induction, increases the blood-sugar; powerful autonomic stimuli from the operation site, as in the present gastrectomy series, increase the blood-

sugar by this means, as Griffith (1923) first showed in animals. Sympathetic stimulation may also be produced by the anaesthetic agent itself, as was shown by Johnson (1949), who studied ether hyperglycaemia in rabbits: in these animals, stabilized after a two-stage adrenalectomy, the rapid and high rise in blood-sugar levels which occurred in the normal animal anaesthetized with ether did not take place; the same was true of the hyperglycaemia due to anoxia. Further, the increase of blood-sugar did not occur with ether or anoxia in normal animals in which a subarachnoid block had been induced to the level of T4, but did appear when the block was lower than T6. Mild or moderate haemorrhage has no effect on the blood-sugar, as was shown by Lawrence and Plaut (1942) in blood donors. The results of the present investigation show that, in operations limited to superficial structures, the blood-sugar is stable in non-diabetic and controlled diabetic subjects anaesthetized with the sequence thiopentone, gallamine, nitrous-oxide:oxygen, pethidine, with full oxygenation maintained throughout. Some increase of blood-sugar occurs in non-diabetic patients when upper abdominal sections are carried out under this technique, but its degree is without clinical importance.

Hypoglycaemia is a rare complication during or after anaesthesia in diabetic patients who have been suitably prepared, and Graham (1945) had seen a delayed return of consciousness due to this cause only once; in this patient there were none of the cardinal signs of hypoglycaemia, and intravenous glucose restored consciousness immediately. The finding that intravenous hexamethonium powerfully potentiates the action of parenteral insulin in anaesthetized man, both diabetic and non-diabetic, is in agreement with the work of Laurence and Stacey (1952) on unanaesthetized patients. The same result obtains in rabbits, and also in dogs (Schachter, 1951). Both Schachter (1951) and Laurence and Stacey (1952) found no consistent effects on the blood-sugar from hexamethonium alone; it is also interesting to note that animals after sympathectomy do not develop hypoglycaemia under natural conditions (Dworkin, 1931). In the present studies, however, the blood-sugar in anaesthetized man was reduced by hexamethonium alone, as shown in Table III. Under conditions of minor stress or activity the basal glycogenolytic level in the normal animal may be raised by nervous mechanisms, the final action of which is probably through the adrenal medulla. It seems that, in the unanaesthetized animal and man, such nervous mechanisms can break through or by-pass the autonomic block induced by hexamethonium; settled general anaesthesia probably prevents such compensations taking place until a lower level of the blood-sugar is reached. This explanation receives support from the association of the hypoglycaemic and hypotensive effects in the present series. Thus where the autonomic block was only partially effective, as indicated by the absence or slightness of action on the blood-pressure, compensatory glycogenolysis, due to release of adrenal medullary hormone secreted in response to nervous stimulation, occurred to some extent as in the normal organism.

The hypoglycaemic reactions—pallor, tachycardia, pupillary dilatation, and profuse sweating, sometimes with muscular tremors—are due to widespread

sympathetic discharge (including an increased liberation of adrenal medullary hormone) generated centrally by the fall in the blood-sugar level (Cannon, McIver, and Bliss, 1924). Animals after sympathectomy are permanently hypersensitive to insulin, the injection of which produces a rapid and precipitous decline in blood-sugar, with no signs of spontaneous recovery, although all the symptoms of hypoglycaemic reaction can appear, usually much earlier and in a much more severe form, sometimes with convulsions (Britton, Geiling, and Calvery, 1928; Dworkin, 1931; McDonough, 1939). In such animals direct excitation of the cerebrum by the very low levels of blood-sugar may account for some of the signs observed. A similar decline of blood-sugar occurred when hexamethonium was given with insulin in Cases 61, 62, and 63, also without evidence of spontaneous correction. Exaggerated signs of hypoglycaemia in the form of profuse sweating and extreme pallor occurred in Cases 1 and 62, but in Cases 2, 61, and 63 the only sign of hypoglycaemia was a progressive tachycardia, without a sharp peak. Hexamethonium also masks many of the classical signs of insulin-induced hypoglycaemia in unanaesthetized man, as Laurence and Stacey (1952) observed, producing only a steadily increasing tachycardia, whereas with insulin alone the heart-rate shows a sharp, high peak.

In patients suffering from peripheral vascular disease, which is a common complication of long-standing diabetes, controlled hypotension is contraindicated. Moreover, the danger of severe hypoglycaemia in producing acute coronary insufficiency or central nervous damage is well known, and it seems that moderate or severe diabetes necessitating insulin therapy is a strong contra-indication to the use of the technique of controlled hypotension by ganglion block with hexamethonium. If there are overwhelming reasons for its use, the insulin dosage before operation must be kept low, and strict watch must be maintained for signs of hypoglycaemia, one of the most constant being a progressive tachycardia. It appears that when such signs are present under these conditions there is a severe degree of hypoglycaemia, and immediate intravenous administration of glucose solution is necessary. Further, because of the necessarily small doses of insulin before operation, greater care than usual must be observed during the recovery period to prevent the onset of hyperglycaemia and ketosis, and it may even be necessary to institute a six-hourly or four-hourly regimen for the first 24 hours after operation.

I wish to thank Professor R. St. L. Brockman, Mr. F. W. Holdsworth, Mr. W. Hynes, and Mr. W. J. Lytle for permission to perform these studies on patients admitted under their care. My gratitude is also due to Dr. A. R. Jordan and the staff of the Department of Biochemistry, United Sheffield Hospitals, for their ready co-operation in the blood-sugar determinations. Miss C. Roseman, Statistician to the Department of Social and Industrial Medicine, University of Sheffield, gave invaluable help in preparing the statistical analysis. Mr. A. S. Foster, Medical Artist, United Sheffield Hospitals, drew the figures. I gratefully acknowledge the encouragement and helpful criticism which I have received from Dr. F. R. P. O'Hara-Proud, Consultant Anaesthetist, United

Sheffield Hospitals, and from Professor E. J. Wayne, Dr. G. M. Wilson, and Dr. D. R. Wood, Department of Pharmacology and Therapeutics, University of Sheffield.

Summary

1. Two cases are described of severe hypoglycaemia occurring in diabetic surgical patients under light general anaesthesia, during which the technique of controlled hypotension with hexamethonium bromide was employed.

2. In investigating these occurrences, experiments under standard conditions gave the following results in selected non-diabetic patients under general anaesthesia: (1) During superficial operations in 20 subjects the blood-sugar remained constant throughout. (2) Upper abdominal section in 10 patients produced a maintained rise of the blood-sugar level which was statistically significant but clinically unimportant. (3) During superficial operations in 25 cases under induced hypotension with hexamethonium bromide, the blood-sugar decreased after hexamethonium was given, remaining stable at this lower level. (4) In two patients hexamethonium greatly potentiated the action of parenteral insulin, causing severe hypoglycaemia.

3. Three patients with controlled diabetes showed a stable blood-sugar with the standard anaesthetic technique. Considerable potentiation of insulin occurred in one further diabetic patient in whom hypotension was induced with hexamethonium.

4. Hexamethonium in the anaesthetized subject masked many of the signs of hypoglycaemia, even when severe. The only constant sign was a progressive tachycardia.

5. The probable mechanisms of the results are discussed, and it is concluded that controlled hypotension with hexamethonium is strongly contra-indicated in diabetic patients.

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THE HAEMATOLOGICAL AND NUTRITIONAL EFFECTS OF GASTRIC OPERATIONS¹

BY J. BLAKE AND P. A. RECHNITZER

(From the Department of Medicine, University of Edinburgh)

THE present study was undertaken in order to ascertain the haematological and nutritional effects of partial gastrectomy, gastroenterostomy, and total gastrectomy. In the case of total gastrectomy it was desired particularly to know whether the operation resulted in the development of a megaloblastic anaemia.

Patients and Methods of Investigation

The patients were divided into three groups according to the type of operation they had undergone: (1) a partial-gastrectomy group of 104, (2) a gastro-enterostomy group of 65, and (3) a total-gastrectomy group of 10 patients. The partial gastrectomy operations were mainly of the Polya type. All patients comprising groups (1) and (2) had had their operations at least three years prior to the present examination. The total-gastrectomy group, on the other hand, was composed of patients in whom the period since operation varied from nine months to three years. In the partial-gastrectomy and gastro-enterostomy series the operation was carried out in all cases for peptic ulcer. In the total-gastrectomy group the operation was carried out for gastric carcinoma in seven cases, for gastric ulcer in two cases, and for cardiospasm in one. In collecting the partial-gastrectomy and gastroenterostomy groups a random sample of 175 patients was chosen from the surgical records of the Royal Infirmary, Edinburgh. Of these patients 142 replied to a letter and reported for examination. Of the remaining 33, 18 were dead, and 15 failed to reply. In addition, 27 women who had had partial gastrectomy were chosen at random from the surgical records of the County Hospital, York, and in this instance all the patients reported for examination. These latter patients were seen through the kind permission of Dr. C. N. Pulvertaft. Omitting the 18 patients known to be dead, the 169 examined constituted a 91.8 per cent. follow-up of the sample originally chosen. In the surgical records of the Edinburgh Hospitals and the County Hospital, York, only 12 patients could be found who had had a total gastrectomy operation and who were still alive. Of these 12 patients 10 reported for examination.

When the patients were seen, a general history was taken with special emphasis on working capacity, external loss of blood, and symptoms which might point to the presence of anaemia or nutritional deficiencies. Then a search for evidence of iron or vitamin deficiency was carried out, and included

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examination of the skin, lips, buccal mucosa, tongue, and nails. The patients were weighed, and the present weight was compared with the average weight two to three years prior to operation as stated by the patient. In estimating loss of weight it was difficult to decide upon the most suitable basic weight for purposes of comparison. As pointed out by Pulvertaft (1952), many patients had, immediately prior to operation, either lost weight as a result of their ulcer, or gained weight owing to rest in bed and milk diet. It was therefore thought that the weight two to three years prior to operation was the best standard with which to compare present weight. Only patients who were reasonably certain of their weight at that time were included in the observations. A difference of 10 per cent. or more of the body-weight was regarded as significant. This difference may be thought too small, because insurance statistics show that, at the time of weighing, a great majority of persons are grossly inaccurate in estimating their weight. Of the patients included, however, more than 70 per cent. were able to state their exact weight recorded two to three years previously, and the remainder were satisfied that the estimate they gave was correct to within four or five pounds. It is possible also that the latter group of patients are more weight-conscious than the average healthy population. Laboratory investigations included a haemoglobin and haematocrit estimation in every case. The haemoglobin estimations were made with a photoelectric haemoglobinometer calibrated so that 14.8 gm. per 100 ml. = 100 per cent. In all patients whose haemoglobin was under 95 per cent. a red-cell and reticulocyte count, and examinations of peripheral blood films and of the nervous system, were made. In all male patients with a haemoglobin level under 90 per cent., and female patients with a haemoglobin level under 85 per cent., a stool benzidine test was performed. The method of investigation of the total-gastrectomy group was similar to that of the other patients, but more extensive in that a red-cell count and reticulocyte count, examination of the peripheral blood film and nervous system, the stool benzidine test, and serum-protein estimations, were done in every case; but in one case it was found impossible to obtain sufficient blood for the protein estimation. Protein was estimated by the micro-Kjeldahl method. In three patients the bone-marrow was examined. For purposes of comparison, haemoglobin and serum-protein estimations for normal male and female subjects were taken from the Medical Research Council Report (1945). The M.R.C. haemoglobin estimations were made with the Haldane haemoglobinometer, in which it is now known that 100 per cent. = 14.8 gm. haemoglobin per 100 ml. of blood, and serum-proteins were estimated by the micro-Kjeldahl technique.

Introduction

The stomach has a double relationship with the haemopoietic system; it secretes hydrochloric acid which facilitates iron absorption (Bruusgaard, 1946; Barer and Fowler, 1937; Moore, Arrowsmith, Welch, and Minich, 1939), and it secretes intrinsic factor which is necessary for normal erythropoiesis (Castle and Locke, 1929; Castle and Townsend, 1929; Castle, Townsend, and Heath,

1930). In view of this relationship it was thought that the removal of part or all of the stomach would tend to cause either iron-deficiency anaemia or megaloblastic anaemia. To discover whether this were true many workers performed gastrectomy operations on animals such as the dog, pig, rat, and monkey, and a hypochromic microcytic type of anaemia developed quite commonly (Ivy, Morgan, and Farrell, 1931; Maison and Ivy, 1933-4; Mullenix, Dragstedt, and Bradley, 1933; Petri and Jensenius, 1941). In no case did megaloblastic anaemia develop (Girdwood, 1950). In spite of the negative experimental results in animals, it was possible that gastrectomy in man might lead to megaloblastic anaemia as well as hypochromic anaemia, and when gastrectomy operations in man became relatively common, this possibility was investigated. There have been many haematological surveys of patients who have had gastric operations of various types, and though a hypochromic microcytic type of anaemia has been found regularly and to a moderately uniform degree, the findings as regards megaloblastic anaemia have been very variable. Taking the three main types of gastric operations in man, gastroenterostomy, partial gastrectomy, and total gastrectomy, we might summarize the findings in the literature by saying that both partial and total gastrectomy cause a fairly high incidence of hypochromic microcytic anaemia, and that the incidence is higher the more radical the gastrectomy (Bruusgaard, 1946; Chiatellino, 1939; Dedichen, 1934; Gordon-Taylor, Hudson, Dodds, Warner, and Whitby, 1929; Lublin, 1936; Lyngar, 1950; Morley and Roberts, 1928; Morley and Bentley, 1938; Scott and Longmire, 1949; Vaughan, 1932, 1938). The anaemia is of greater severity in women than in men. Gastroenterostomy causes only a mild degree of hypochromic microcytic anaemia. All these surveys are open to the criticism that they were not performed on true random samples. Most of the patients examined had reported to hospital because of symptoms due to anaemia or to complications following their operations, while many patients who were symptom-free were not included in the surveys.

All investigators are agreed that gastroenterostomy and partial gastrectomy cause megaloblastic anaemia in a negligible number of patients, so that difference of opinion in the case of this form of anaemia relates to total gastrectomy only. The earlier reports were of single cases of megaloblastic anaemia following total gastrectomy (Hartman, 1921; Hartman and Eusterman, 1935; Moynihan, 1911; Meyer, Schwartz, and Weissman, 1941); later, more comprehensive surveys gave very variable results (Bethell, Sturgis, Rundles, and Meyers, 1945; Beebe and Meneely, 1949; Goldhamer, 1933; Hurst, 1932; MacDonald, Ingelfinger, and Belding, 1947; Pack and McNeer, 1943). Some of these surveys reported the incidence as negligible (Pack and McNeer, 1943; Scott and Longmire, 1949), while others reported it to be very high (Bethell, Sturgis, Rundles, and Meyers, 1945; Goldhamer, 1933; MacDonald, Ingelfinger, and Belding, 1947). One cause of this difference of opinion is the variable interval between operation and the haematological survey. This interval has tended to be short in most surveys, since total gastrectomy is done almost exclusively for gastric carcinoma. It seems in general that the longer the interval after operation the

higher is the incidence of megaloblastic anaemia, and in some cases it appears that the anaemia takes as long as 10 years to develop. Another source of confusion springs from the criteria used in diagnosing megaloblastic erythropoiesis. It is universally agreed that macrocytic anaemia and megaloblastic anaemia are not synonymous, but in reviewing the literature it is often difficult to know whether or not megaloblastic anaemia is meant when the term 'macrocytic' is used. Many investigators have based a diagnosis of megaloblastic anaemia on examination of the peripheral blood, and even this examination has often been incomplete, undue diagnostic significance being attached to the colour index, which can be very misleading if dissociated from the other more specific indices. Since only megaloblastic erythropoiesis is of significance in estimating deficiency of the anti-megaloblastic principles, and since bone-marrow examination is the only sure and simple diagnostic means of discovering megaloblastic erythropoiesis, more frequent bone-marrow examinations would be desirable. The procedure is often not feasible as part of a survey, and on this account it has been carried out on relatively few occasions. Only when the interval after operation has become as long as eight or 10 years, and marrow examinations are performed more frequently, can the true incidence of megaloblastic anaemia after gastric operations be estimated. Nutritional surveys of patients who have undergone gastric operations have not been made frequently, and the evidence available suggests that, apart from the deficiency of iron and the anti-megaloblastic principles, the degree of nutritional deficiency which occurs is not of serious consequence (Pulvertaft, 1952).

Observations

The observations made in the present survey fall under the headings of haematology and nutrition. The haematological results will be described first. For purposes of presentation the patients will be segregated into the three groups of gastroenterostomy, partial gastrectomy, and total gastrectomy, and of these three the partial gastrectomy group will be discussed first. Of the 104 patients who had had partial gastrectomy 50 were male and 54 female. It appears advisable to deal with these separately, and the male patients will be described before the female. The haemoglobin distribution in the male patients is shown in Fig. 1, in which the abscissa represents haemoglobin percentage marked off in intervals of 5 per cent. and the ordinate represents the percentage distribution of subjects showing the various haemoglobin levels. Cross-hatched columns represent the patients, and white columns represent the normal male population as given in the Medical Research Council Report (1945). It can be seen by comparing the two groups that the patients show evidence of anaemia, as demonstrated by a shift of their haemoglobin levels to the left of the normal group. The arithmetic mean of the haemoglobin levels in normal men is 102.2 per cent., while the mean level in the patients is 92.9 per cent. A comparison of the distributions by means of the χ^2 test shows that the data for the patients and the M.R.C. data for male subjects could not belong to the same population ($\chi^2 = 72.014$, degrees of freedom 16). This highly significant

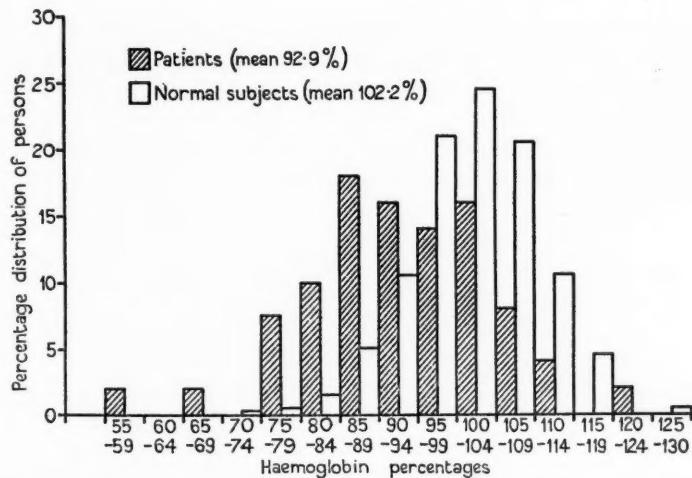


FIG. 1. Percentage distribution of haemoglobin levels among male partial-gastrectomy patients, compared with the distribution among normal men (M.R.C. Report, 1945).

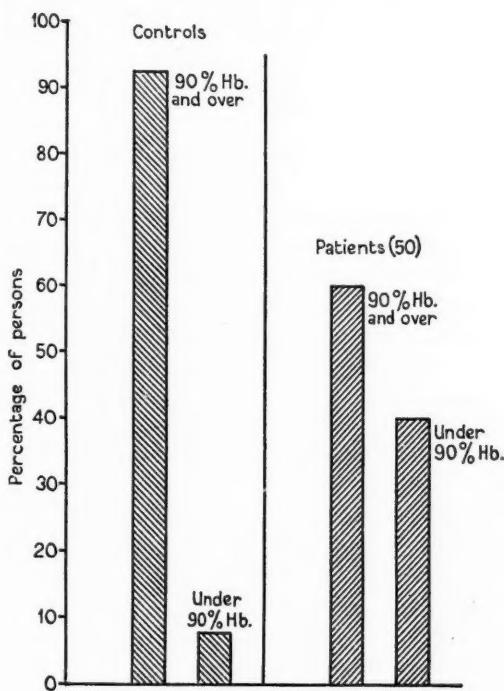


FIG. 2. Comparison of male partial-gastrectomy patients with controls, taking 90 per cent. haemoglobin as 'anaemia threshold'.

difference between the two groups is due to the fact that a large proportion of patients had haemoglobin levels in the interval 75 per cent. to 90 per cent. The degree of anaemia may be more readily appreciated from Fig. 2. Here 90 per cent. haemoglobin has been taken as an arbitrary anaemia threshold for men; the two columns in the left half of the figure show the percentages of normal men, and the two columns on the right the percentages of patients, in

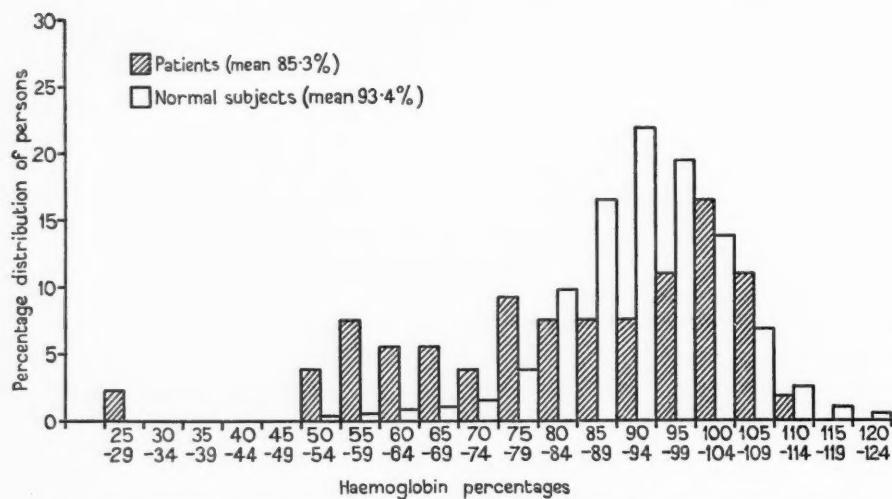


FIG. 3. Percentage distribution of haemoglobin levels among female partial-gastrectomy patients, compared with the distribution among normal women (M.R.C. Report, 1945).

whom the haemoglobin level was above and below 90 per cent. It can be seen that only 7·5 per cent. of normal men showed haemoglobin values under 90 per cent., while 40 per cent. of the patients showed such values. This difference is highly significant, being more than three times the standard error of the percentages relating to the patients. All the anaemic male patients had a hypochromic, microcytic type of anaemia, with a colour index ranging from 0·69 to 0·96.

Turning now to the 54 female patients who had had partial gastrectomy, and analysing them in the same way, we can see from their haemoglobin distribution, as illustrated in Fig. 3, that they give a complex pattern showing a very wide haemoglobin distribution. A considerable portion of the distribution is shifted to the left in comparison with the haemoglobin distribution of normal women as taken from the M.R.C. Report. This shift suggests an increased incidence of anaemia in the patients. The χ^2 test applied to the two distributions shows that the M.R.C. normal women and the patients could not belong to the same population ($\chi^2 = 84\cdot835$, degrees of freedom 20). The difference arises mainly from the large proportion of patients whose haemoglobin levels fall within the interval 50 per cent. to 70 per cent. The mean of the haemoglobin values among the patients is 85·3 per cent., while among normal women

it is 93.5 per cent. Another method of demonstrating the presence of anaemia is to take an arbitrary anaemia threshold, as was done in the case of male patients, and compare the percentage of normal women below this level with the percentage of patients below it. In the case of women an anaemia threshold of 85 per cent. haemoglobin has been taken, and Fig. 4 shows that 17.5 per cent.

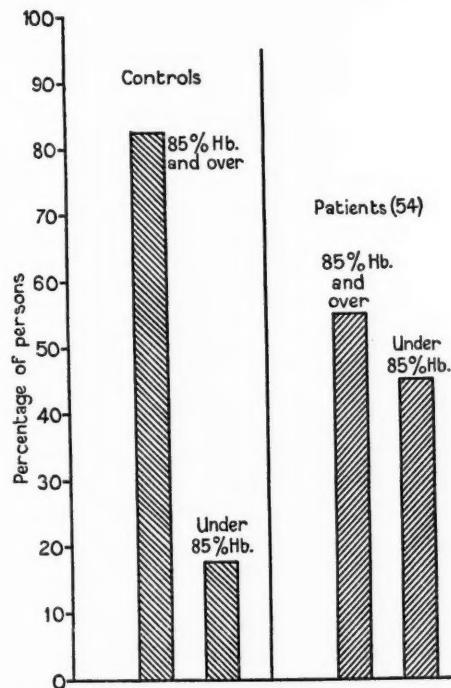


FIG. 4. Comparison of female partial-gastrectomy patients with controls, taking 85 per cent. haemoglobin as 'anaemia threshold'.

Haemoglobin Levels at Intervals of 5%

Age (years)	Under 50%	50-54%	55-59%	60-64%	65-69%	70-74%	75-79%	80-84%	85-89%	90-94%	95-99%	100-4%	105-9%	110-14%
25-29														
30-34														
35-39	1		1		1	1	1	1					1	1
40-44	1	11	1	1	1	1	1	1	1	1	1	1	1	1
45-49	1							1	1	1	11			
50-54		1	1		1	1		1		1	11	1	1	1
55-59						1				1		1		
60-64		1				1	1		1	1	11	1	11	
65-69								11	1			1	11	
70-74													11	
75-79														

FIG. 5. Scatter diagram showing haemoglobin levels related to age in women who had undergone partial gastrectomy.

of the normal female population had haemoglobin values below 85 per cent., while 45 per cent. of the patients had such values. This difference is highly significant, being more than three times the standard error of the percentages relating to the patients. In Fig. 3 it can be seen that the patients show a very similar haemoglobin distribution. A scatter diagram of these patients, arranged according to haemoglobin levels in intervals of 5 per cent. and age in

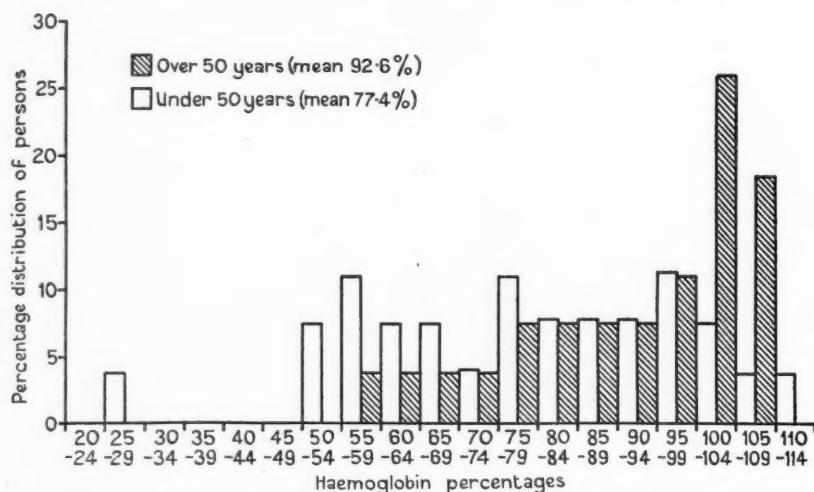


FIG. 6. Comparison of haemoglobin distribution among female partial-gastrectomy patients over 50 years and under 50 years.

intervals of five years, is given in Fig. 5, and shows that their haemoglobin levels tend to increase with age. It was thought that the onset of the menopause might be an important factor in bringing about this increase in haemoglobin percentage with age, and so, in an attempt to analyse these results further, the patients were divided into those over and those under 50 years of age. There were 27 women in each group. Fig. 6 provides a comparison between the haemoglobin levels in the two groups, and it can be seen that the under-50-years group is more anaemic than the over-50-years group. The arithmetic mean for the haemoglobin in the women under 50 years is 77.4 per cent., while in those over 50 years it is 92.6 per cent. The χ^2 test shows that the under-50-years group could not belong to the same population as the M.R.C. normal women ($\chi^2 = 104.892$, degrees of freedom 20). The difference between the under-50-years group and the M.R.C. women is due to a relative concentration of the former in the haemoglobin interval 50 per cent. to 70 per cent. On the other hand the over-50-years group and the normal women could have been taken from the same population ($\chi^2 = 25.531$, degrees of freedom 18).

Fig. 7 compares the percentages of the three groups (M.R.C. normal women, female gastrectomy patients over 50 years, and female gastrectomy patients under 50 years), showing haemoglobin levels under 85 per cent. It can be seen

that 17.5 per cent. of normal women had haemoglobin values under 85 per cent., while 30 per cent. of the over-50-years patients and 59 per cent. of the under-50-years patients had levels below 85 per cent. The difference between the younger patients and the normal women is highly significant in that it is more than three times the standard error of the percentages relating to the younger patients. The difference between the older patients and the normal women is

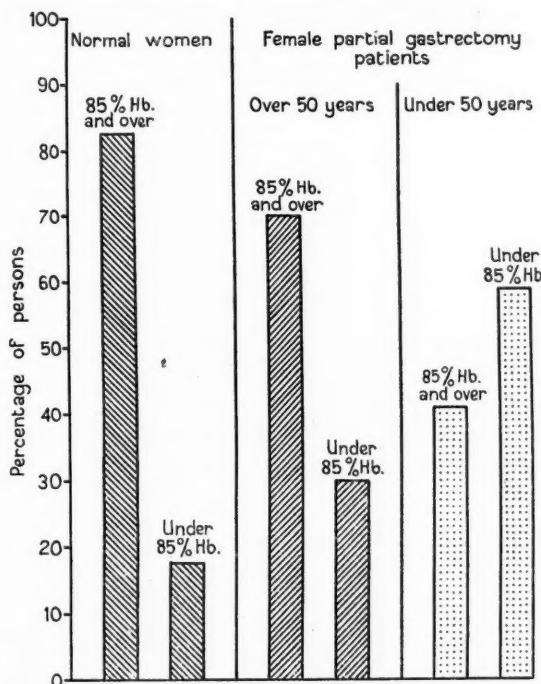


FIG. 7. Comparison of normal women and female partial-gastrectomy patients over 50 years and under 50 years, taking 85 per cent. haemoglobin as 'anaemia threshold'.

not significant, though in this respect it must be remembered that the M.R.C. 'normal' women showed a rather high incidence of anaemia. Thus the patients under 50 years old were considerably more anaemic than those over 50 years, and this conclusion is confirmed by the fact that the difference between the percentages of patients in each group whose haemoglobin was under 85 per cent. is significant, being more than twice the standard error of the difference. The lower haemoglobin values in the younger women can probably be correlated with loss of iron associated with menstruation, pregnancy, and childbirth.

All the women who had had partial gastrectomy and were anaemic had a hypochromic, microcytic type of anaemia, except one who had a megaloblastic anaemia as proved by marrow examination. Whether the latter patient's anaemia is the result of her operation, or fortuitously associated with it, cannot

be said definitely. Since she had a peptic ulcer prior to her operation, it is more likely that the megaloblastic erythropoiesis developed as a result of her operation. The anaemia after partial gastrectomy in male and female patients was not due to bleeding from the alimentary tract, since there was no history of

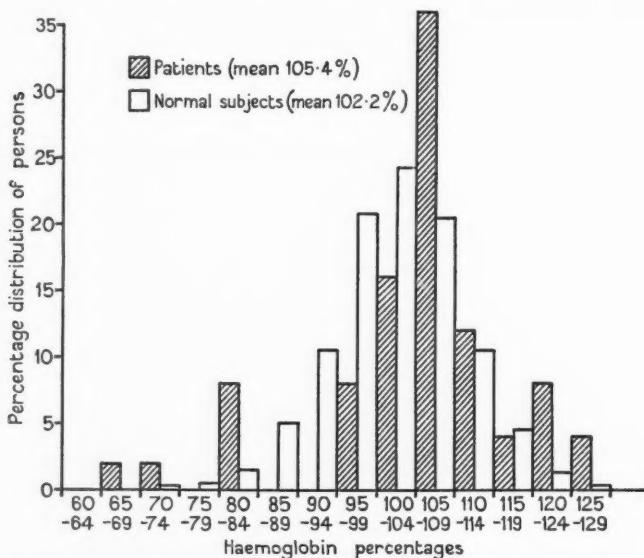


FIG. 8. Percentage distribution of haemoglobin levels among male gastroenterostomy patients, compared with the distribution among normal men (M.R.C. Report, 1945).

such loss of blood, and stool benzidine tests, which were carried out in all cases of anaemia, were found positive in only four.

In the gastroenterostomy group there were 50 male and 15 female patients. In the case of male patients, it can be seen from Fig. 8 that their haemoglobin distribution is not very different from that of normal men in the main range, but shows a marked irregularity at the extremes. When the distributions of the two groups are compared, the χ^2 test shows that no significance can be attached to any apparent difference between them. The relative arithmetic means are 105.4 per cent. for the patients and 102.2 per cent. for the controls. This seems to indicate that, if anything, the patients have higher haemoglobin values than the controls. In this connexion it must be remembered that the M.R.C. study, from which control figures were taken, was done in 1943, when the diet was more restricted than it is at present. In the 15 women who had had gastroenterostomy there was again no evidence of anaemia as compared with the M.R.C. findings for normal women. Fig. 9 shows that the distribution of the patients' haemoglobin values is not very different from that of the normal values, tending if anything towards a higher figure. The corresponding means are 97.8 per cent. for the patients and 93.5 per cent. for the controls. The χ^2

test shows that the two groups could well belong to the same population ($\chi^2 = 13.386$, degrees of freedom 20). Again it might be pointed out that, as in the case of the male subjects, the diet in 1943, when the control figures were collected, was poorer than at present. In addition, all the women who had had

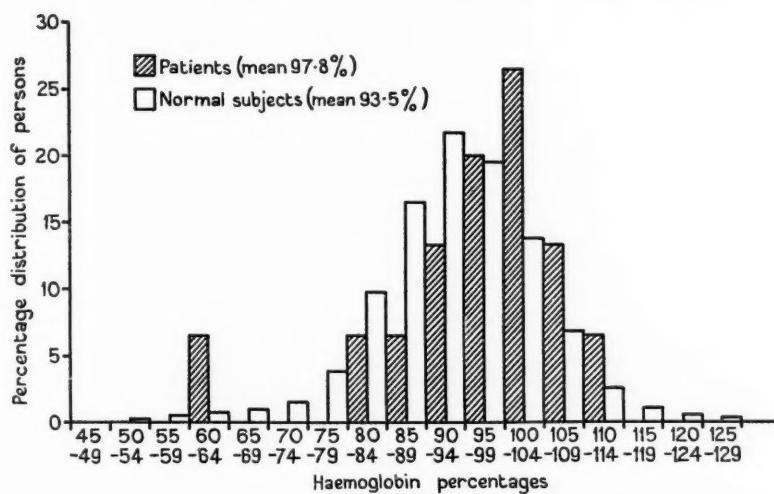


FIG. 9. Percentage distribution of haemoglobin levels among female gastro-enterostomy patients, compared with the distribution among normal women (M.R.C. Report, 1945).

gastroenterostomy, except two, happened to be above the child-bearing age. In view of this fact, and since the women of child-bearing age were responsible for the high incidence of anaemia among the female patients who had had partial gastrectomy, it would be unwise to conclude that gastroenterostomy does not increase the liability to anaemia in women below the age of 50.

The last set of haematological findings to be presented relates to the 10 men who had had total gastrectomy. Fig. 10 provides a comparison of their haemoglobin levels with those of normal men. Evidence of the presence of anaemia in these patients is indicated by a shift of their haemoglobin distribution to the left. The mean haemoglobin value for the patients is 88.3 per cent., compared with 102.2 per cent. for normal men. The number of patients is too small to permit statistical analysis of the haemoglobin distribution. Taking 90 per cent. haemoglobin as the anaemia threshold for men, we can see from Fig. 11 that only 7.5 per cent. of the normal male population had haemoglobin values below 90 per cent., while 60 per cent. of the patients had values below 90 per cent. This is a highly significant difference, being more than three times the standard error of the percentages relating to the patients. Table I shows additional data regarding the 10 patients. In the case of the total-gastrectomy group many patients showed macrocytic red blood-cells, so that, in order that the true incidence of anaemia might be discovered, an anaemia threshold based on the

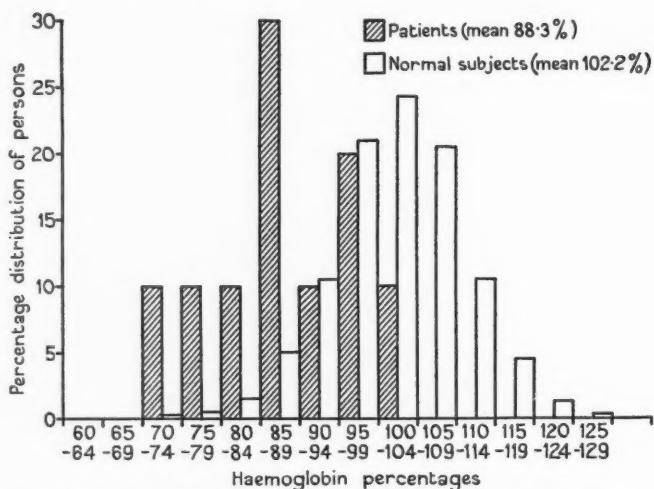


FIG. 10. Percentage distribution of haemoglobin levels among male total-gastrectomy patients, compared with the distribution among normal men (M.R.C. Report, 1945).

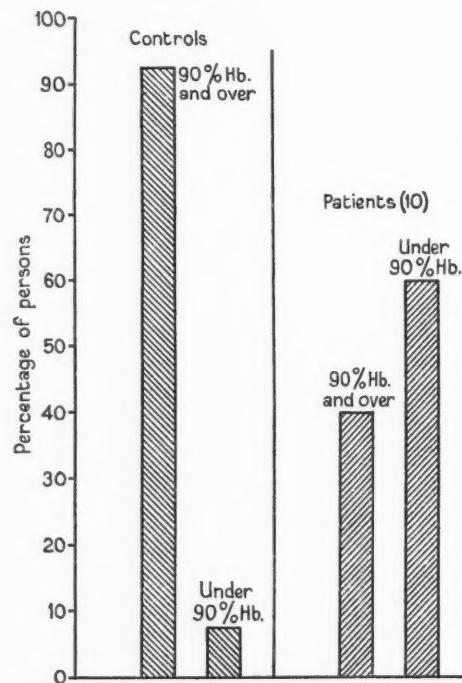


FIG. 11. Comparison of total-gastrectomy patients with controls, taking 90 per cent. haemoglobin as 'anaemia threshold'.

TABLE I
Haematological Findings after Total Gastrectomy

Case number	Age (years)	Hæmoglobin (%)	Red blood-cells (millions per c. mm.)	Colour index	Mean corpuscular volume (c.c.)	Mean corpuscular haemoglobin concentration (%)	Bone-marrow	Location	Time since operation	Serum-protein (gm. per 100 ml.)
1	58	73	2.8	1.3	117.8	32.4	Mainly normoblastic; some 'transitional' megaloblasts	Gastric carcinoma	2½ years	6.93
2	74	75	3.2	1.17	109.3	31.7	Mainly normoblastic; some 'transitional' megaloblasts	Gastric carcinoma	3 years	6.87
3	70	96	3.6	1.3	113.8	34.6	Not examined	Gastric ulcer	3 years	5.89
4	62	88	3.7	1.2	108.1	32.5	Not examined	Gastric carcinoma	1 year	6.81
5	50	94	4.1	1.1	100	33.1	Mainly normoblastic; some 'transitional' megaloblasts	Gastric ulcer	2½ years	7.09
6	36	85	4.1	1.0	100	30.7	Not examined	Gastric carcinoma	2½ years	6.13
7	53	84	4.9	0.8	81	31.1	Not examined	Gastric carcinoma	2 years	5.86
8	45	89	4.6	0.96	86.9	32.9	Not examined	Cardiospasm	9 months	Not examined
9	46	101	5.2	0.97	82.6	34.7	Not examined	Gastric carcinoma	1½ years	6.45
10	56	98	4.8	1.0	84.3	35.8	Not examined	Gastric carcinoma	2 years	6.51

NOTE. Since submission of the present paper another patient has been investigated after total gastrectomy. Seven years prior to examination a 45-year-old woman had undergone total gastrectomy for a simple gastric ulcer which was thought to be malignant. The patient developed a severe macrocytic anaemia with a classical megaloblastic marrow, which responded to vitamin B₁₂.

red-cell count had to be taken in addition to the usual threshold based on the haemoglobin level. This second threshold has been taken arbitrarily at a level of 4.5 million red cells per c. mm. of blood. The first six patients in Table I are seen to have a macrocytic anaemia, as shown by a red-cell count below 4.5 million per c. mm. and a mean corpuscular volume of 100 c. μ or more. It was possible to perform bone-marrow examinations in only three patients, Cases 1, 2, and 5, and in these the marrow showed 'transitional' types of megaloblasts, which suggest that a partial deficiency of anti-megaloblastic principles was present (Innes, 1948). The high incidence of macrocytic anaemia (60 per cent.) in the total-gastrectomy patients is in sharp contrast to those who had partial gastrectomy, among whom only one instance of macrocytic (in this case definitely megaloblastic) anaemia was found in a total of 104. In addition, the interval between operation and examination in the cases of partial gastrectomy was three years or more, whereas in those of total gastrectomy it was three years or less. It is possible that, given a longer interval after operation, many more of these patients who had had total gastrectomy would develop a macrocytic (and probably a megaloblastic) anaemia. In addition to the six patients with macrocytic anaemia there were two others (Cases 7 and 8) with haemoglobin levels below 90 per cent. The mean corpuscular volumes and mean corpuscular haemoglobin concentrations show that one of these patients (Case 8) had a normochromic normocytic anaemia, and the other (Case 7) had a hypochromic normocytic anaemia. Thus, of the whole group of 10 patients, eight had an anaemia of one kind or another. None of the total-gastrectomy patients had either a history of external loss of blood or a positive stool benzidine test.

Nutritional survey

In addition to the haematological investigations a nutritional survey was undertaken. Table II shows the investigations carried out and the results obtained. In the left-hand column are tabulated certain clinical findings which are believed to be of nutritional significance, and which are grouped under the headings of malnutrition and subnutrition. The other columns show the incidence of these findings among the patients, who are arranged according to type of operation and sex. Evidence of malnutrition was looked for in the form of iron deficiency, and of vitamin deficiency as evidenced by buccal, dermal, neurological, and haematological changes. Subnutrition was estimated on the basis of loss of weight, diminished working capacity, and, in the case of the total-gastrectomy patients, serum-protein levels.

It can be seen that, apart from the cases of megaloblastic anaemia already described, the evidence for vitamin-B deficiency was negligible. Of the 50 men who had had partial gastrectomy two showed angular stomatitis, cheilosis, and glossitis. Both these patients, however, had an iron-deficiency anaemia, so that the signs noted may possibly have been due to sideropenia rather than deficiency of vitamin B (Brown, 1949; Darby, 1946; Witts, 1931). Of the 54 women who had had partial gastrectomy one showed megaloblastic anaemia and two showed angular stomatitis. Both these patients had an iron-deficiency anaemia, and

TABLE II
Nutritional Findings

Effects of operation	Partial gastrectomy		Gastroenterostomy		Total gastrectomy	
	Men	Women	Men	Women	Men	Women
Vitamin-B deficiency	2/50 (4%)	Total incidence	3/54 (5.5%)	Total incidence	0	Total incidence
Glossitis	2/50 (4%)	Glossitis	0	Glossitis	0	Glossitis
Angular stomatitis	2/50 (4%)	Angular stomatitis	2/54 (4%)	Angular stomatitis	0	Angular stomatitis
Chelosis	2/50 (4%)	Chelosis	0	Chelosis	0	Chelosis
Skin changes	0	Skin changes	0	Skin changes	0	Skin changes
Megaloblastic anaemia	0	Megaloblastic anaemia	1/54 (2%)	Megaloblastic anaemia	0	*Megaloblastic anaemia
Neurological changes	0	Neurological changes	0	Neurological changes	0	Neurological changes
Iron deficiency	Iron deficiency anaemia 40%	Iron deficiency anaemia 45%	Not present	Not present	Not present	Iron deficiency anaemia 20%
Malnutrition	2/44 (4.5%)	10/43 (23.2%)	1/46 (2.2%)	1/11 (7.7%)	5/10 (50%)	6/10 (60%)
Subnutrition	†Number of patients having lost weight	20/53 (37.7%)	7/50 (14%)
Serum-protein (mean)	6.5 gm. per 100 ml.

* In these three patients the marrow showed 'transitional' megaloblasts.

† Based on patients' statements that their present weight was less by 10 per cent. (or more) than their weight two to three years prior to operation.

‡ Working capacity was assessed on patients' statements.

both wore dentures. It appears that either dentures or iron deficiency can account for angular stomatitis, without any vitamin-B deficiency. There was no evidence of vitamin-B deficiency in the gastroenterostomy series. Of the 10 patients who had had total gastrectomy, one (Case 2) showed angular stomatitis. This again was of doubtful significance, since the patient wore dentures. In addition he had a megaloblastic anaemia, so that any element of iron deficiency would be difficult to detect. In the total gastrectomy group six patients are tabulated as having a macrocytic anaemia. Only three of these cases were proved to be megaloblastic, so that vitamin-B deficiency can be postulated in only these three. No patient of any group showed evidence of other vitamin deficiency. Iron deficiency, as manifested by anaemia, has been dealt with in the haematological section. It appeared also as koilonychia, but only in two patients. These two were women who had had a partial gastrectomy, and both had an iron-deficiency anaemia. Comparing present body-weight with the body-weight two to three years before operation, we found the proportion of patients who had lost 10 per cent. or more of their weight to be as follows: partial gastrectomy, two out of 44 men (4.5 per cent.) and 10 out of 43 women (23.2 per cent.); gastroenterostomy, one out of 46 men (2.2 per cent.) and one out of 13 women (7.7 per cent.); total gastrectomy, five out of 10 patients (50 per cent.). Patients who had had partial gastrectomy showed a greater loss of weight than those who had had gastroenterostomy, and those who had had total gastrectomy showed the greatest loss of all. Seven of the 10 total gastrectomy operations, however, were done for gastric carcinoma, so that the role played by these operations in the loss of weight becomes rather obscure. Many patients were not able to state their weight two to three years prior to their operations, and so had to be omitted from the weight survey. Working capacity was assessed on patients' statements, and undoubtedly this introduced certain fallacies. Judging the evidence as carefully as was possible, we found that working capacity was diminished in 16 per cent. of men and 37.7 per cent. of women who had had partial gastrectomy, 14 per cent. of men and 26.6 per cent. of women who had had gastroenterostomy, and 60 per cent. of patients who had had total gastrectomy. It was diminished more frequently after partial gastrectomy than after gastroenterostomy, though in the male patients the difference was too small to be of any significance. It was diminished most frequently in the total-gastrectomy group. A notable feature of the working-capacity survey was the much commoner occurrence of diminished working capacity in women than in men. This difference was noticed previously by Pulvertaft (1952). Serum-protein estimations were carried out in nine of the 10 patients who had had total gastrectomy. The 10th patient (Case 8) had such poor veins that it was impossible to obtain sufficient blood for a protein estimation. The results are shown in the right-hand column of Table I, where it can be seen that they range from 5.86 gm. to 7.09 gm. per 100 ml. Table II shows the mean to be 6.5 gm. per 100 ml. These results are within normal limits as shown by the Medical Research Council (1945) findings, in which normal men (blood-donors) had a mean serum-protein value of 6.57 gm. per

100 ml., with a minimum of 5.63 gm. and a maximum of 7.59 gm. per 100 ml. All the nine patients had a normal albumin-globulin ratio except one (Case 2), in whom the ratio was reversed. Correlation between the various aspects of malnutrition and subnutrition was looked for, but was not found. Nor was there a correlation between signs of undernutrition and anaemia, apart from the fact that vitamin deficiency was found only where there was anaemia. The signs noted as suggesting vitamin deficiency (apart from megaloblastic anaemia) were so few, and of such doubtful significance, that this association becomes unimportant.

Discussion

If the anaemia threshold in men is taken as 90 per cent. haemoglobin, and in women as 85 per cent. haemoglobin, it is seen that women over 50 years, and men of all ages, who undergo partial gastrectomy for peptic ulcer develop an iron-deficiency anaemia to a somewhat similar extent. The actual figures found were 40 per cent. for men and 30 per cent. for women. On no occasion was the anaemia of severe degree. Of women under 50 years, however, 59 per cent. developed an iron-deficiency anaemia, and in one case the haemoglobin was as low as 27 per cent. In all cases this anaemia responds to iron therapy, so that the condition cannot be regarded as being of serious consequence. Only one out of a total of 104 patients who had had partial gastrectomy developed a megaloblastic anaemia. It cannot be stated definitely whether this anaemia was coincidental with the operation or resulted from it.

In the whole partial-gastrectomy group there was negligible evidence of malnutrition, and the signs of subnutrition were not of serious significance. Gastroenterostomy was not found to cause anaemia of any type, nor to produce undernutrition to a serious degree.

The 10 patients who had had total gastrectomy differed from the others in that they showed a very high incidence of anaemia (80 per cent.), which in six cases was of the macrocytic type. Of these six cases, it was demonstrated in only three that the marrow was megaloblastic. It was not feasible to examine the marrow in the other three patients, so that it cannot be said whether their anaemia was macronormoblastic or megaloblastic. A point suggesting that it was megaloblastic is that the three patients who were proved to have megaloblastic anaemia were the only three who had marrow examinations, and they were chosen for reasons of convenience rather than because their haematological findings differed from those of any of the other patients who had macrocytic anaemia. These megaloblastic anaemias after gastrectomy respond to liver therapy (Goldhamer, 1933; Hartman and Eusterman, 1935; MacDonald, Ingelfinger, and Belding, 1947; Meyer, Schwartz, and Weissman, 1941). In addition to the six patients who had macrocytic anaemia, two others had anaemia; this was normochromic and normocytic in one case, and hypochromic and normoeytic in the other. Apart from patients who, by their anaemia, showed deficiency of iron and the haemopoietic principle, the evidence for malnutrition was negligible. Subnutrition was manifested in 50 per cent. of

total-gastrectomy patients as a loss of 10 per cent. or more of their weight recorded two to three years before operation, and in 60 per cent. as diminished working capacity. Serum-protein levels were within normal limits in nine of the 10 patients, and the albumin-globulin ratio was normal in all except one, in whom it was reversed. The significance of this single case of protein reversal is not clear.

It is concluded that undesirable haematological or nutritional sequelae do not occur so frequently or severely as a consequence of partial gastrectomy or gastroenterostomy as to contra-indicate these operations when they are therapeutically indicated. The same conclusions are reached as regards total gastrectomy operations, for, though the sequelae are more frequent and severe, they are largely remediable. Nevertheless, they are sufficiently serious to indicate great caution in advising the operation for non-malignant conditions.

The authors wish to express their gratitude to Professor Davidson, under whose supervision this survey was carried out. They would also like to thank the Surgeons in the Royal Infirmary, Edinburgh, who permitted them to see their cases; Dr. Pulvertaft, through whose kindness and co-operation they were able to see 27 patients at the County Hospital, York; and Dr. Guthrie Scott, who helped during the initial stages of the investigation. Finally they wish to thank Dr. Lilli Stein, who advised on the statistical analysis of the results.

Summary

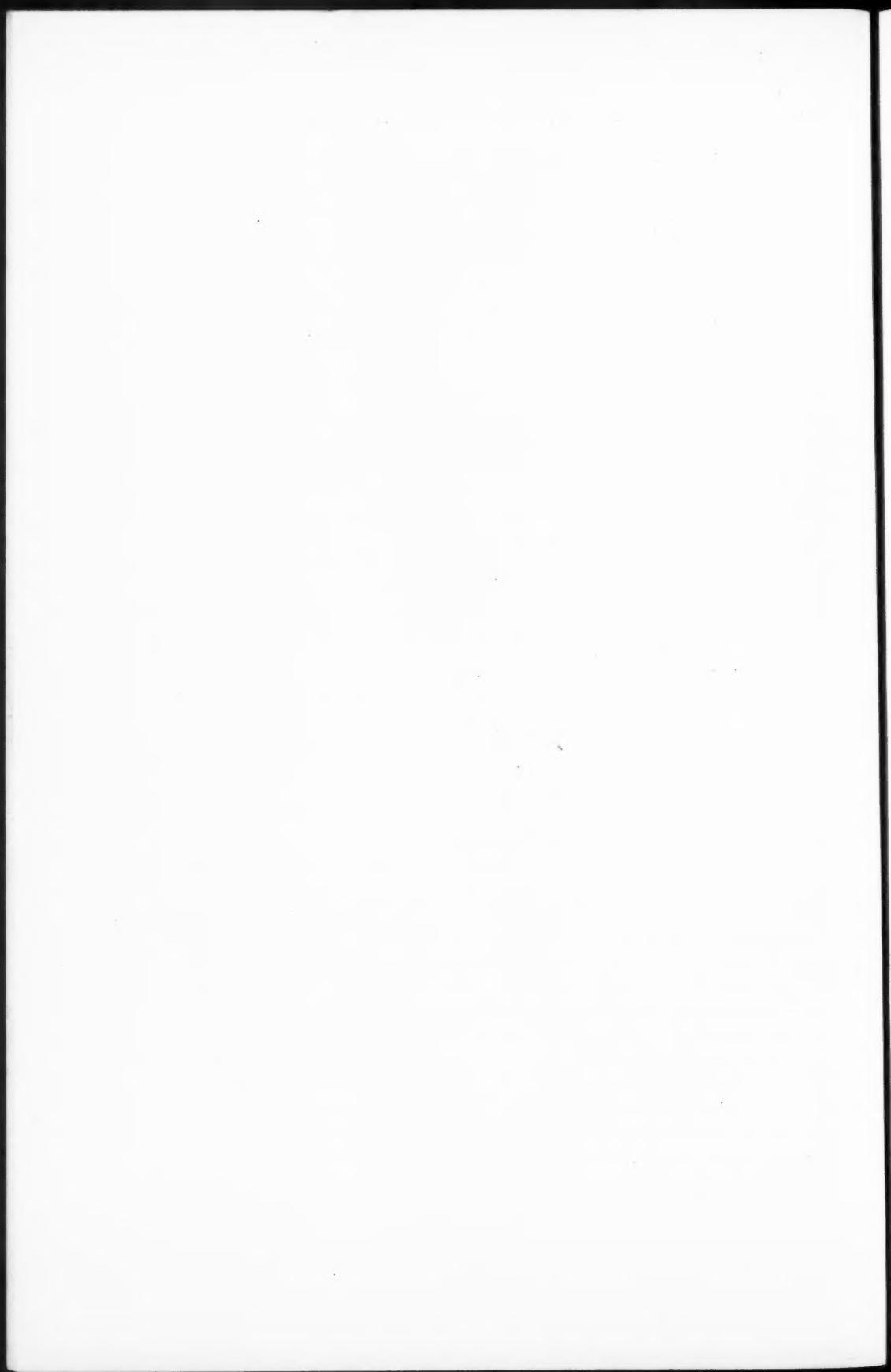
1. An investigation of 104 patients (50 male and 54 female) who had undergone partial gastrectomy, 65 patients (50 male and 15 female) who had undergone gastroenterostomy, and 10 (all male) who had undergone total gastrectomy, was carried out with a view to discovering the incidence and type of anaemia and the incidence of undernutrition after these operations.
2. In the partial-gastrectomy group, iron-deficiency anaemia occurred in 40 per cent. of the male and 45 per cent. of the female patients. There was no evidence of anaemia in the gastroenterostomy group. In the total-gastrectomy group only 20 per cent. (two out of 10 patients) can be said definitely to have shown iron-deficiency anaemia. Megaloblastic anaemia occurred in one woman who had had partial gastrectomy, and in none of the gastroenterostomy patients. In three of the total-gastrectomy patients who had a macrocytic anaemia, marrow examination showed the presence of 'transitional' megaloblasts. Three other total-gastrectomy patients also had a macrocytic anaemia, but it was not possible in their case to perform bone-marrow examinations.
3. Evidence of malnutrition (vitamin-B deficiency) was present in 4 per cent. of the men and 5.5 per cent. of the women who had had partial gastrectomy, in none of the gastroenterostomy patients, and in 30 per cent. (three out of 10) of those who had had total gastrectomy. Evidence of subnutrition appeared as significant loss of weight in 4.5 per cent. of men and 23.2 per cent. of women who had had partial gastrectomy, in 2.2 per cent. of men and 7.7 per cent. of

women who had had gastroenterostomy, and in 50 per cent. (five out of 10) of patients who had had total gastrectomy. Subnutrition as shown by diminished working capacity occurred in 16 per cent. of men and 37·7 per cent. of women who had had partial gastrectomy, in 14 per cent. of men and 26·6 per cent. of women who had had gastroenterostomy, and in 60 per cent. (six out of 10) of patients who had had total gastrectomy.

4. These undesirable sequelae are neither so severe nor so frequent as to contra-indicate operation where it is therapeutically indicated.

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THE EFFECT OF DIET AND REGULAR LIVING CONDITIONS ON THE NATURAL HISTORY OF PEPTIC ULCER¹

BY JAMES W. RAE AND R. S. ALLISON

IN the Royal Navy peptic ulcer was one of the chief causes of invaliding during the last war, and this constant loss of trained men caused the Admiralty to establish an experimental scheme for the rehabilitation and employment of men with healed peptic ulcers. The scheme is described briefly in the *Medical History of the Second World War* (1952), while a detailed account has been given elsewhere (Rae, 1947). The experiment allowed us to observe a group of patients under controlled environmental and dietetic conditions for a period of over 12 months. We have also been able to make a follow-up study of most of the patients at least five years after they left our care. In the present paper the results of our observations are considered in relation to the following questions:

1. Can patients with healed peptic ulcers do a full day's work under medical supervision and dietetic control?
2. What is the natural history of patients with healed peptic ulcers when under strict dietetic control with regular meals and medical supervision? Do they remain free from the symptoms and signs of ulcer?
3. What beneficial, curative, or preventive influences may be attributed to regular meals and special diet?
4. What factors contribute to or cause a relapse of the disease?

Conditions of the Experiment

The patients selected for the experiment were all men whose services were of value to the Navy on account of their special knowledge and training. Throughout the period of observation the following conditions were fulfilled:

1. The men lived together as a corporate unit, had their own messing arrangements, and were under the care of one medical officer.
2. Their diet was arranged on the lines generally accepted for patients with healed ulcers; they were provided with extra milk and eggs, and indigestible foods were excluded. Meal-times were regular, and snacks were provided between the main meals. Furthermore, if a man's symptoms recurred he could be given a light diet for a few days without having to be admitted to hospital.
3. Every man was provided with employment according to his training and experience. Casual or makeshift work was not allowed. A full normal day's duty was carried out, the only restrictions being that the men were not moved about from one place to another; they were employed only on shore and harbour

¹ Received February 26, 1953.

duties, and were excused from overtime or work involving exceptional physical hardship.

4. The men were interviewed by the medical officer at least once weekly at a time which did not interfere with the daily working routine. At this interview they were weighed, any symptoms were noted, and treatment was prescribed if necessary. They were also encouraged to discuss any problems of a personal nature, or any difficulties connected with their working and living conditions. The interviews were informal, and took place in a room adjacent to the living-quarters, so that the atmosphere of a sick parade was avoided.

Patients Selected

Only patients with proved peptic ulcers were selected for the scheme, and they were given a preliminary period of hospital treatment until they were free

TABLE I
Nature of Lesion: 63 Cases of Chronic Peptic Ulcer

<i>Number of patients</i>	<i>Gastric ulcer</i>	<i>Duodenal ulcer</i>	<i>Jejunal ulcer</i>	<i>Gastro-enterostomy (old duodenal ulcer)</i>	<i>Total</i>
.	14	47	1	1	63
<i>History of complications:</i>					
Perforation	5	14	19
Haematemesis or melaena	4	10	1	..	15
Pyloric stenosis	1	1
<i>Total</i>	<i>9</i>	<i>24</i>	<i>1</i>	<i>1</i>	<i>35</i>

TABLE II
Formal Intelligence Tests (Shipley and Wechsler)

<i>Result</i>	<i>Percentage of group</i>
Very superior	5
Superior	29
Bright normal	22
Average	40
Dull normal	4

of symptoms. Men of obviously neurotic or unstable personality, and others who were unwilling to continue serving, were rejected. The experimental group as originally selected consisted of 70 men, but for various non-medical reasons it was only possible to follow for a year the clinical course of the disease in 63 cases. The nature of the lesion in the 63 cases is shown in Table I, together with the incidence of previous complications. It is seen that there was a history of a major complication in 35 patients, or 55.5 per cent., in the majority of whom there were also positive radiological findings. The diagnosis in the 28 uncomplicated cases was confirmed by the demonstration of an ulcer crater at some time during the history. In selecting the patients, emphasis was also placed on the importance of accepting only men of good intelligence and high morale, who were willing to continue their service in the Navy. During the preliminary examination in hospital formal intelligence tests were carried out by the Psychiatric Department. The results are summarized in Table II.

Working Capacity of the Group

When the records were reviewed at the end of the experiment, it was found that nearly half of the men had lost no time off duty on account of dyspepsia, and that about a quarter had been off work for a week or less (Table III). In Table IV the time lost through recurrence of symptoms is shown in comparison with the possible number of working days, together with published figures relating to the insured population of Scotland during 1936-7 (Department of Health for Scotland, 1939). Although no exact comparison can be made between

TABLE III

<i>Number of patients</i>	<i>Percentage of group</i>	<i>Sickness due to dyspepsia</i>
29	46	Nil
17	27	1-7 days
8	12.7	8-21 days
9	14.3	Over 21 days

TABLE IV

	<i>Number of patients</i>	<i>Possible working days</i>	<i>Days off owing to dyspepsia</i>	<i>Percentage loss of working time</i>	<i>Average incapacity per patient</i>
Men employed in R.N. scheme 1944-5 who were off duty with symptoms of recurrence of peptic ulcer	34	9,879	733	7.41	21.5 days
Insured population of Scotland 1936-7: men under 55, incapacitated on account of peptic ulcer (excluding chronic cases in which sickness lasted the whole year)	3,382	1,229,357	203,044	16.52	60.04 days

the naval and civilian figures, there appears to be little doubt that the experiment was of value in preventing incapacitating symptoms in the patients observed. Their capacity for work was, however, appreciably less than that of the general population of naval ratings in the base at which the group was employed. More serious relapses were probably prevented by the arrangements which enabled a man to have a lighter diet, with or without a short period of rest, whenever his symptoms became more severe. Half of the patients who relapsed had a previous history of perforation or haemorrhage, and symptoms tended to be more severe and of longer duration in the age-groups over 30 years than in the younger men. In only nine patients, or 14 per cent., did the time lost through sickness reach the formidable proportions presented by the insured population of Scotland and by the series of Post Office workers reported by Bashford and Scott (1935). With regard to non-dyspeptic illnesses, it was observed that mild recurrences of dyspepsia were often associated with, or followed, upper respiratory infections such as the common cold and sinusitis. This was particularly noticeable during the winter months, when the weekly incidence of dyspeptic symptoms showed an appreciable increase. The relationship

between respiratory and other infections and the recurrence of the symptoms of peptic ulcer has been recognized for many years (Moynihan, 1912; Hurst and Stewart, 1929).

Results

Investigations at the end of the experiment. At the close of hostilities in Europe the men were readmitted to hospital for investigation and resurvey prior to discharge from the Service. The results were assessed, and a barium-meal examination and gastric analysis were carried out in all cases. All the patients were convinced that they had derived benefit from the scheme. Nearly three-quarters of them were under the standard weight for their age and height at the

TABLE V
Results of Resurvey (63 Cases)

GROUP I.	Symptom-free ; normal X-rays and gastric analysis	5 cases (8%)
GROUP II.	Symptom-free ; normal X-rays, but persistent hyperchlorhydria	25 cases (39·7%)
GROUP III.	Symptom-free, but X-rays abnormal, and usually persistent hyperchlorhydria	18 cases (28·5%)
GROUP IV.	Symptoms still present ; X-rays abnormal, and usually persistent hyperchlorhydria	13 cases (20·6%)
GROUP V.	Symptoms still present ; X-rays and gastric analysis normal	2 cases (3·2%)

time of selection for the experiment. At the time of resurvey the average net gain in body-weight per man was just over half a stone, individual gains ranging from three or four pounds to 28 pounds, and with one or two exceptions all the men who were originally under-weight had made good the loss. Complete freedom from symptoms was claimed by 48 of the 63 patients, that is, a proportion of 76 per cent. Judging from this fact, and by the good record of the group as a whole, we expected that a considerable number would show no radiological or other abnormality on reinvestigation. The results, however, showed that this was not the case. It is evident from Table V that about half the patients (31 out of 63) showed persistent radiological signs of abnormality. In most cases these signs were accompanied by persistent hyperchlorhydria, with a high fasting level of acidity and defective neutralization. There were only five patients without symptoms and with no evidence of radiological or chemical abnormality. Twenty-five were symptom-free and had normal X-rays, but were shown to have persistent hypersecretion on gastric analysis. There was thus convincing proof of the absence of any defect of gastro-duodenal function in only 8 per cent. of the whole group. If, however, we add to this figure those patients who had no symptoms or abnormal radiological signs (Group II, Table V) the proportion of men in whom there was no evidence of active ulceration is approximately 48 per cent. With only two exceptions, all who still complained of definite symptoms were found to have some abnormality of motor or secretory function on radiological or test-meal examination. The chief interest lies in the group of patients in whom there was still some radiological abnormality. In most instances actual ulcer crater were demonstrated. In others the duodenal cap

was persistently deformed, but it was thought prudent to include all such abnormal X-ray findings in the category of active or unhealed ulcers, in view of the fact that all the patients had previously shown definite evidence of active ulceration.

The natural course of the disease. The classical account of duodenal ulcer (Moynihan, 1912) suggests a clear-cut clinical picture which is easy and accurate of diagnosis. Many of the recent war-time studies of peptic ulcer, however, reveal conflicting views on the natural history of the disease and on the relationship between symptoms and the presence or absence of an active ulcer. Thus Gill, Berridge, and Jones (1942) stated that the absence of the classical type of remission in the history is significant in distinguishing duodenitis from ulcer on clinical grounds. On the other hand, Love (1943) found that only 50 per cent. of patients with active ulcers had typical remissions, while a similar percentage, with no radiological signs of ulcer but with similar pain, gave the typical history of remissions. Love concluded that, so far as clinical diagnosis is concerned, peptic ulcer can be accompanied by almost any type of dyspeptic pain. In a series of 131 cases, one of us (Allison, 1943) showed that there was a considerable overlap in the incidence and frequency of symptoms between patients showing unequivocal radiological evidence of active ulceration and those with negative findings. Visick (1949) also noted that many patients with a typical clinical history of peptic ulcer show no radiological evidence of a lesion, while many with atypical histories are found to have active ulcers.

In the present series a study of the case histories, and of the weekly records throughout the 12 months of the experiment, has shown that the clinical picture could be divided into three main groups.

1. The first and largest group gave the familiar history of recurrent, dull, aching, or gnawing pain in the epigastrium after meals, relieved by food and by alkalis, and with remissions of variable extent. The symptoms during an attack might range from severe pain to very mild discomfort after meals or between meals. The constant and most characteristic feature of this group was the history of remissions.

2. The second group comprised a much smaller number of men who were rarely free from dyspepsia while under observation, and who complained of a variety of symptoms, such as ill-defined abdominal pain or vague discomfort in the epigastrium, nausea, regurgitation, flatulence, or heartburn. This class contained the over-conscious type of man, the food faddists, and the regular consumers of alkalis and patent medicines, many of whom displayed mildly obsessional traits. No remissions, in the accepted sense of the term, were seen in this group, and it appears from the results of our subsequent investigations that this type of patient may continue to complain of symptoms of dyspepsia long after the clinical and radiological evidence has indicated healing of the ulcer. Gill (1947) has pointed out the unreliability of pain as an index of healing, and it is now generally agreed that the disappearance of pain does not necessarily mean that an ulcer is healing. That the converse may also be true is suggested by the findings in some of the cases in this group.

Case 13. Engine-room artificer, aged 43 years. Dyspepsia began at 27 years. He entered the Navy as a volunteer reservist in September 1939, when 38 years old. His symptoms were aggravated by sea-sickness. He was admitted to hospital in November 1943, when radiography showed a duodenal ulcer. He joined the experimental scheme in June 1944, and was observed for a year. Throughout this period he complained constantly of minor dyspeptic symptoms, although he continued to gain weight and lost no time off duty. Reinvestigation at the end of the test period showed no evidence of active ulceration, but a very high degree of hyperchlorhydria was still present. He was a sensitive, excessively conscientious man of average intelligence, in whom emotional factors appeared to play a large part in determining symptoms. He had an excellent service record, and carried out responsible and even arduous duties in spite of his symptoms. There was a family history of dyspepsia. He had been employed in six or seven different trades, after leaving school, before he finally settled down as a marine engine fitter at the age of 26 years. One might infer from this history that as a young man he reacted to difficulties or frustration by changing his job, but that as he became older and assumed family responsibilities he was forced by economic considerations to settle in a regular trade. Within 12 months, however, he developed dyspepsia, and eventually a peptic ulcer.

Case 15. Able seaman, aged 35 years. At the age of 32 years he began to have attacks of vague epigastric discomfort after meals. Symptoms occurred every three or four months, and lasted for about a week at a time. He entered the Navy in 1941. The attacks became more severe, and he now had regular pain after meals. Investigation in October 1943 revealed a duodenal ulcer, and he was recommended for home shore service. Symptoms continued, and he was transferred for work under the scheme in June 1944, and was observed for 12 months. He missed no duty, but complained of frequent epigastric discomfort and flatulence. There was no real remission of symptoms during the period of observation. His weight remained constant, and when he was resurveyed in June 1945 there was no radiological evidence of active ulceration, although symptoms were still present.

Case 18. Able seaman, aged 38 years. He gave a history of three years of dyspepsia before admission to hospital in March 1944 with a perforated duodenal ulcer. He continued to have symptoms of dyspepsia after operation, and radiography in July 1944 showed persistent spasm of the prepyloric region, which could be temporarily relaxed by pressure. There was persistent deformity of the duodenal cap, but no ulcer crater could be identified, and there was no local tenderness. His symptoms persisted throughout the next 12 months, but he lost no time off duty. At the end of this period there was no radiological evidence of active ulceration. Gastric analysis showed a high fasting acidity and defective neutralization. He was a thin, over-anxious type of man, who became easily depressed and frustrated. Psychogenic factors may thus have played a part in determining the symptoms, which had been almost continuous since his perforation, in spite of prolonged medical treatment and rehabilitation.

3. In a small group of patients there was no history of symptoms until a perforation or haemorrhage occurred. After a further period of freedom from symptoms such patients not infrequently developed the clinical picture of typical ulcer dyspepsia. Although a history of previous dyspepsia may be obtained in the majority of cases of perforation (Black, 1933; Illingworth, 1947), there appears to be a small group of patients who have chronic ulcers which

remain symptomless between each complication. Alvarez (1943) suggested that there is a diminished sensitivity to pain in such cases, so that symptoms are not noticed, or remain minimal, until a complication occurs. That there may be a large number of symptomless ulcers was suggested by Gibbs (1946), who found that of 219 patients with peptic ulcer seen in a series of 2,301 consecutive autopsies, 58.5 per cent. had not complained of dyspepsia during life. In the present series threatened perforation was suspected in three patients who developed acute abdominal pain after a long period of freedom from symptoms, but no actual perforation was seen during the working period of the scheme. Another man, however, developed a perforation shortly after admission to hospital for resurvey at the end of the experiment. This patient had had a perforation 14 months previously, and the second operation revealed a chronic duodenal ulcer which had probably never healed, although he had had no symptoms between the two perforations. Three patients were admitted to hospital during the period of observation on account of haematemesis or melaena. One other man remained completely free of symptoms while under observation, although he still had a duodenal ulcer with a well-marked crater, his only previous symptoms having been two major haemorrhages, each of which followed a period of anxiety.

The first and third of these clinical types have been recognized clearly enough in the past, but the group with continuous symptoms has received little attention. Love (1943) analysed the symptoms of 358 soldiers with dyspepsia, and found that in 90 per cent. of cases abdominal pain was the presenting symptom. This could be divided into (1) post-prandial pain, (2) continuous pain, and (3) pain unrelated to food. It was found that 48 per cent. of patients with active duodenal ulcers complained of post-prandial pain relieved by food and alkalis, but that only 27 per cent. of men suffering from this type of pain had active duodenal ulcers, and in the symptom-complex of this type there appeared to be nothing to distinguish the patients with ulcers from those in the same group with no radiological signs of ulcer. Other characteristics of this group were a high incidence of hyperchlorhydria and a low incidence of neurosis, whereas there was a high incidence of neurosis in the patients who had continuous pain. Some of the latter, who might appear to be the most typically neurotic, were found to have active ulcers, and many men with gastric ulcers complained of this type of pain. An exact pathological diagnosis was considered to be of no importance from the point of view of handling and disposal of this group. Our experience agrees closely with these findings.

Management of the three main groups in relation to recurrence of symptoms. In the present series any patient who came to us with a recurrence of regular pain after meals, with relief by food, nocturnal pain, and loss of weight, was regarded as requiring a period of rest and strict treatment. It was considered that these features were unlikely to occur together except in the presence of an active ulcer. When the cases were reviewed at the end of the experiment, however (Table V), the results only served to confirm the view that the symptoms of gastro-duodenal dyspepsia do not necessarily coincide with the presence of an

active ulcer. The management of the three main clinical groups is summarized in Table VI, while Table VII shows the complications and relapses of the whole series. It is seen that the loss of working time in the group of patients with continuous symptoms (Type II) was more than double that of the first group. This difference was confirmed by comparing the individual patients in the two groups, since there was very little difference between their actual relapse-rates.

TABLE VI
Management of Patients in the Present Series

<i>Type of case</i>	<i>Chief features</i>	<i>Treatment</i>
I. Typical recurring attacks of gastro-duodenal dyspepsia		Regular medical supervision. Lighter diet for a few days when symptoms recurred. Phenobarbitone. Failure of symptoms to respond, especially if accompanied by loss of weight and night pain, led to admission to hospital
II. Continuous atypical symptoms, with no remissions in the accepted sense		Regular medical supervision and sorting out of neurotic symptoms
III. No symptoms until a complication threatened. (Three cases of haematemesis or melena; three cases of suspected perforation. No ulcer actually perforated, but one later perforated in hospital while the patient was awaiting resurvey)		Regular medical supervision. Admission to hospital when a complication threatened

TABLE VII

<i>Type of case</i>	<i>Number of patients</i>	<i>Previous history of major complications</i>		<i>Patients who relapsed</i>	<i>Percentage loss of working time in cases of relapse</i>	<i>Average incapacity per relapse</i>
		<i>Perforation</i>	<i>Haemorrhage</i>			
I (Typical)	48	11	12	26	6.3	15.6 days
II (Continuous symptoms)	11	6	1	7	13.2	39.5 days
III (No symptoms between complications)	4	2	2	*1 (haemorrhage)	15.5	53 days (1 case)

* One patient also had a perforation while awaiting resurvey in hospital.

From the point of view of management, there was no doubt that the patients in the second group required much greater individual attention than those in the other two groups.

Possible causes of relapse and failure to heal. In the present series the various factors which have been suggested as possible causes of recurrence were studied, and have been reviewed in detail elsewhere (Rae, 1947). Only the main conclusions will be considered here. In analysing the results at the end of the experiment (Table V), the 30 men who had no symptoms and no signs of abnormality on X-ray examination were contrasted with the 31 men who showed persistent abnormal radiological signs, especially in relation to the following points: age, length of previous history, incidence of major complications, nature of the original lesion, and loss of working time on account of dyspepsia (Table VIII). The age, duration of previous symptoms, and incidence of previous complications appear to have no bearing in this particular series on the healing

of the lesion, but gastric ulcers on the whole appear to have done better than duodenal ulcers.

What significance can be attached to mechanico-chemical, toxic, and psychogenic factors in causing failure of ulcers to heal? It has been generally agreed that the inability to tolerate ordinary Service rations was one of the main reasons for the early breakdown in the armed forces of dyspeptic persons who had subjected themselves to dietetic restrictions in civilian life (Payne and Newman, 1940; Allison, 1941; Wade, 1942). The diet provided for the men

TABLE VIII

<i>Results of resurvey</i>	<i>Number of patients</i>	<i>Average age (years)</i>	<i>Average length of history</i>	<i>Incidence of major complications</i>	<i>Original lesion</i>	<i>Average time of sickness per man during period of observation</i>
No symptoms, and no signs of abnormality on X-ray examination	30	31	6.4 years	53% {Gastric ulcer 9 Duodenal ulcer 21}	10 days	
Persistent X-ray abnormality, often with evidence of active ulceration	31	29	5.35 years	53% {Gastric ulcer 4 Duodenal ulcer 26 Jejunal ulcer 1}	8.5 days	

employed in the Royal Naval scheme conformed to the orthodox conception of the dietetic treatment of peptic ulcer. Since it was estimated that over 90 per cent. of the meals provided in the special mess during the year the men were under observation (excluding leave periods) were actually consumed, it could not be said that *dietetic indiscretions* played any important role. Yet it was observed that a recurrence of symptoms frequently followed a period of leave. There may well have been indiscretions during leave; long train journeys may have upset the routine of regular meals, or additional psychogenic influences may have come into play during the leave period. Whatever may be the explanation, it appeared that in many cases interruption of the regular routine promoted the return of symptoms. *Defective teeth* played no part in causing symptoms, since all the men had good dental health on being first selected for the experiment. There is no evidence that *irregularity of meals* or watch-keeping played any significant part in the aetiology of peptic ulcer in the Royal Navy. It is of interest that Bashford and Scott (1935) considered that irregularity of meals and hours of work were probably of less importance than was usually supposed. This view has recently been confirmed by Doll and Jones (1951). There remained the variable factors of *tobacco and alcohol*, and the degree of co-operation attained with the men in these respects, the factor of personality or temperament, and the influence of worry or other psychological causes in inducing chronicity. A comparison of the two groups from these aspects gave the results shown in Table IX. It is seen that here again there is no significant difference between the two groups. Stable personalities were more numerous among the men who had no symptoms or signs of gastric or duodenal abnormality at the end of the test period. The difference is slight, however, and the men had been carefully selected in the first instance with a view to excluding

grossly abnormal types of personality. This being so, the frequency of smoking and continued indulgence in alcohol will be remarked. Some trouble had been taken to impress upon the group as a whole the possible effects of such habits in determining chronicity of symptoms, and it is interesting therefore to note how ineffective was this advice, although the men were all of good intelligence, and for the most part willing, stable, and co-operative in other respects. We can

TABLE IX

Result of resurvey	Number of patients	Consumption of		Co-opera- tion	Person- ality and tempera- ment	to gastric symptoms	<i>Psycho- genic factors related to</i>
		Tobacco	Alcohol				
No symptoms and no signs of ab- normality on X- ray examination	30	Nil . 3	Nil . 5	Good 22	Stable 24	30%	
		Moderate 21	Moderate 19	Fair 8	Unstable 6		
		Excessive 6	Excessive 6	Poor 0			
Persistent X-ray ab- normality, often with evidence of active ulceration	31	Nil . 2	Nil . 8	Good 22	Stable 22	38%	
		Moderate 19	Moderate 16	Fair 8	Unstable 9		
		Excessive 10	Excessive 7	Poor 1			

only conclude that a considerable proportion of the men were unable to effect the necessary mental adjustment to give up these habits.

Long-term Value of the Experiment

The original object of the experiment was fulfilled, in that most of the men were enabled to continue giving good service to the Navy as the result of the special conditions which were provided for them. With a view to determining whether the natural history of the disease had been in any way modified by such a prolonged period of medical supervision and regular living conditions, we have recently attempted to make a follow-up survey of the patients who took part in the experiment. The minimum follow-up period is five years since the men left our care, and six years since they first came under our observation. It should be noted that all patients were given a full course of medical treatment in hospital before being accepted for employment under the special conditions, and those who still had evidence of active peptic ulceration at the end of the experiment were given a further period of strict medical treatment before returning to civilian life.

Follow-up method. As our patients were widely scattered after leaving the Navy, the only possible method of follow-up was by postal questionnaire. Such a method can never be entirely satisfactory, but the replies were in most cases supplemented by personal letters, and the information so obtained, together with our previous knowledge of the individual patients, has enabled us to present what we believe to be a reasonably accurate picture.

Results of follow-up. Fifty-two men out of 63 replied to the questionnaire (Table X). Of those who were traced, 48 were in the United Kingdom and Eire, two had emigrated (one to Canada and one to U.S.A.), one was still serving

in the Royal Navy on a long-term engagement, and one was serving in the Middle East in another government service.

Assessment of ulcer activity in the traced patients. In their review of a series of cases of peptic ulcer after 10 years, Martin and Lewis (1949) considered that a history of characteristic ulcer dyspepsia during the last five years was sufficient evidence of activity, and the absence of such symptoms was accepted as evidence of inactivity. Since we believe that symptoms alone are not necessarily reliable

TABLE X
Follow-up of Patients

Type of ulcer	Traced	Untraced	Total
Gastric	11	3	14
Duodenal	39	8	47
Jejunal	1	..	1
Gastro-enterostomy (old duodenal ulcer)	1	..	1
Total	<u>52</u>	<u>11</u>	<u>63</u>

TABLE XI
Loss of Working Time during Follow-up Period

Average time off work per year on account of dyspepsia	Number of men	%
Nil	10	19
1-7 days	10	19
8-21 "	22	43
Over 21 "	10	19

as a guide to the activity of an ulcer, we prefer to record simply the severity and frequency of such symptoms, without attempting to be dogmatic about the activity or inactivity of the lesion. Of the 52 patients traced only four were completely free from dyspepsia during the previous five years. Five had experienced symptoms only on very rare occasions, while 43 had been subject to recurrent symptoms which were severe enough to cause all except one to be off work at some time during the follow-up period (Table XI). Thirty-two of the patients traced, or half of the original group, were off work for more than a week every year on account of dyspepsia, and a third of this number lost more than three weeks a year.

Complications. Four patients had a history of subsequent complications; two had had melaena, both having a previous history of at least one haemorrhage; one man had had a perforation, and another had developed pyloric stenosis and was awaiting operation at the time of the follow-up.

Natural history during follow-up period. When the replies were analysed it was found that the histories fell into five groups according to the frequency and severity of symptoms (Table XII). It is seen that two-thirds of the patients fell into two groups (B and C) which differed only in the length of the remissions between recurrent attacks of typical ulcer dyspepsia. When the five groups were considered in relation to the time lost off work, it was found that Groups B

and C accounted for more than half of the men who had more than a week's sickness each year, and for most of those who had over three weeks' sickness. All but two men of Group B, and every man in Group C, lost some time off work on account of dyspepsia, so that there was a close relationship between the frequency of attacks and the time lost through the disease. When Group D was studied it was found that, whereas this group showed the greatest loss of time off duty while under regular observation in the special unit, the average yearly

TABLE XII
Symptoms during Follow-up Period

<i>Group</i>	<i>Features</i>	<i>Number of men</i>
O	No symptoms	4
A	Symptoms very rarely experienced	5
B	Long remissions (over three months)	18
C	Frequent attacks (remissions of less than three months)	18
D	Frequent or constant minor dyspepsia	7

incapacity was now much less, and compared more favourably with the other groups. Seven of the 11 patients originally placed in this category were traced, and only two were off work for more than a week per year during the follow-up period; four were sick only on occasional odd days, while one man lost no time off work in spite of constant symptoms. During the original test period it was noticed that the members of this group appeared to derive the most benefit from the regular régime. Of those who were traced, only one had abandoned the use of alkalis. Three had given up all forms of dieting, and four still dieted regularly; two continued to take alkalis regularly, while four took medicine only when symptoms were severe. In the other groups it was found that a third of the patients who had long remissions (Group B) still dieted regularly, while a similar number still took alkalis fairly regularly; the patients who were subject to more frequent attacks of dyspepsia (Group C) showed a larger proportion who still followed some kind of régime. Nearly two-thirds of the latter group dieted or took alkalis regularly, while only two or three men had given up all forms of treatment. As was to be expected, the four men who had remained completely free from symptoms (Group O) had abandoned all forms of treatment. The remaining patients of the other groups dieted or took alkalis only when symptoms returned. To summarize, over two-fifths of the patients who were traced still followed a fairly regular régime of diet and alkaline powders, while one-fifth had given up all forms of treatment. The remaining two-fifths took alkalis, combined with diet in about half the cases, only when symptoms recurred. The majority of the men who still followed a fairly regular régime belonged to the groups in which periodic symptoms had continued.

Possible causes of relapse. Half of the men related the recurrence of symptoms to worry, but many also remarked that irregular meals, or carelessness with diet, tobacco, or alcohol might aggravate their dyspepsia, while the remainder stated that the attacks appeared to occur without any obvious precipitating cause. A further question was asked regarding any special worries during the

previous five years in connexion with family affairs, housing problems, money matters, illness of the patient or his near relatives, work, or unemployment. Analysis of the replies showed that only half of the men who related their symptoms to worry had had any specific anxiety under these headings. Many noticed that, although they had no major worries, they found that trifling matters upset them. Several interesting comments were made in this connexion, for example: 'I have no serious worries, but little things worry me a lot. . . I know I am very easily worried, and the more I try to calm down the worse I seem to get.' Another man noticed that nervous tension would aggravate his symptoms, although he had no outstanding worries. Yet another made the following observations: 'I notice that these attacks seem to coincide with some important event in my social life . . . which suggests to me some emotional cause somewhere.' These findings suggest that when anxiety is a prominent feature it may be regarded as a personality-trait rather than a specific external influence. A question regarding the average amount of tobacco and alcohol consumed showed that the majority of men still smoked and drank in moderation, in spite of the recurrence of symptoms in many cases. It is thus doubtful whether these factors can have had much influence on the natural history of our cases.

Prognosis in relation to previous history. When the case records were completed at the end of the original period of observation in 1945, we attempted to assess the probable prognosis in each case. In making such an assessment we were guided not only by the history and clinical findings, but also by the patient's personality and his general attitude towards his disease. When our records came to be compared with the results of the follow-up survey, it was found that in most cases we had been able to give a reasonably accurate prognosis. Thus all cases now classified in Groups O and A (Table XII) were originally given a good prognosis. On the other hand, in nearly half of the cases now placed in Groups C and D a note had been made that the ulcers were likely to recur. Most of the patients in Group B had followed their expected course of fairly long remissions. One patient now in this group had previously been subject to frequent attacks accompanied by vomiting, and had been noted as a probable candidate for surgical treatment in the near future, but this forecast proved to be wrong. The patient who was awaiting operation for pyloric stenosis at the time of the follow-up had, on the other hand, been given an excellent prognosis at the end of the test period.

Discussion

From the results of the follow-up survey it was evident that the majority of the patients dieted or took alkalis regularly only when their symptoms recurred. This agrees with the conclusion of Martin and Lewis (1949) that the natural course of the peptic ulcer is the main factor which determines whether the patient will persevere with treatment. When it is remembered that our patients had lived under a common régime for at least a year while under observation, and that they had a better understanding of their condition than the average hospital patient, these findings serve to support our previous conclusion (Rae,

1947) that the natural history of the disease was not influenced to any appreciable extent by such a lengthy period of treatment and rehabilitation. It has already been remarked (Table III) that no less than 54 per cent. of the original group suffered from a recurrence of symptoms severe enough to cause incapacity for duty at some time during the period of observation. Although half of the patients who relapsed were off duty for only a week or less, the relapse-rate corresponded closely to that found by Gainsborough and Slater (1946) in their series. These authors found that medical treatment was disappointing, not with regard to the healing of the ulcers, but in the prevention of relapses after return to work. They recommended that attention should be paid in the follow-up period to the adjustment of work conditions, including the use of resettlement facilities under the Disabled Persons (Employment) Act, 1944, and to the careful discussion with the patient of his social and psychological problems. These conditions were fulfilled by the régime which was provided for our patients, with the important exception that the men were living away from home and remained under naval discipline. Care was taken, however, that no man was retained in the scheme against his will, while the necessary help was arranged for any who had family or psychological problems. Again, in view of the careful selection of patients, why should there have been a relapse-rate of over 50 per cent. during the test period, and of nearly 70 per cent. during the next five years? These facts appear to indicate that the natural history of the disease is responsible for a formidable rate of recurrence even under the most ideal conditions of after-care. Illingworth (1945) stated that, on a long-term assessment, both medical and surgical treatment fail to effect a cure in over 40 per cent. of cases, while the experience of Raimondi and Collen (1946) suggests that the recurrence-rate of symptoms in patients treated for peptic ulcer is remarkably constant. Ingelfinger and Moss (1945) considered that some ulcers will recur, no matter how carefully the patient is handled, but they believed that a suitable régime will in a large number of cases reduce the chances, frequency, and severity of recurrences. While there is little doubt that the régime which was followed enabled most of our patients to continue giving satisfactory service to the Royal Navy—and this, after all, was the original object of the experiment—it is doubtful whether the small group of patients whose ulcers appeared to be symptomless between complications would have suffered any great disadvantage under ordinary Service conditions. The arrangements whereby a patient could be given a short period of rest on a lighter diet were of value in preventing more serious relapses in some members of the largest group (Type I, Table VI), but the patients who seemed to derive the greatest benefit from the régime were those who had almost constant minor symptoms. The diet and regular living conditions, contrary to expectations, did not appear to be of primary importance, and our experience showed that the most valuable feature of the scheme was the regular interview between patient and medical officer. Although the patients with continuous symptoms appeared, individually, to benefit most from the régime, this group had the highest sickness-rate during the test period. The position was reversed during the follow-up period, as this type of patient seemed

to do much better in civilian life than the members of the other two groups. Two explanations suggest themselves to account for this difference. Abnormal personality-trait were more common in this group, so that psychological influences may have played a more prominent role under Service conditions than in civilian life. The frequency of minor symptoms may also cause this type of patient to take much greater care of himself, and thus to report sick more often.

It is obvious that no scheme of management can be successful without the full co-operation of the patient. If, as seems likely, relatively few patients are able to follow a regular régime, it might be expected that the relapse-rate of unselected cases of peptic ulcer would be much greater than that of a carefully selected group living under controlled conditions. It has been shown above, however, that this was not so, the relapse-rate of our patients being similar to other published figures. That it was the will to work which made the men continue to work, rather than the rapid healing of their ulcers, is suggested by the results of re-examination at the end of the test period (Table V). Goldbloom and Schildkrout (1944) studied a group of cases of peptic ulcer in the United States Army, and found that there was a close correlation between the morale of the patients and the results obtained. All the available evidence suggests that, when the patient with an ulcer continued to give useful military service, the important feature was not the question whether he had received medical or surgical treatment, but the fact that he had a stable personality and was anxious to remain well and continue serving. Good selection and morale were probably the reasons why Wakeley (1944) found that a large proportion of men who had had perforated peptic ulcers were still serving in the Navy many years after operation.

Todd (1952) has recently challenged the orthodox methods of management of the disease in vigorous terms, and Lawrence (1952) concluded that dietetic treatment, as at present practised, does not hasten the healing of the ulcer, and may even delay it. In the present series the fact that less than one-tenth of the men were free of all symptoms and signs of gastro-duodenal trouble, after living for a year under circumstances in which most of the usually accepted exciting causes of peptic ulcer had been eliminated, challenges the validity of such 'causes' and of the elaborate régimes which are based on them. The wisdom of handing out standardized instructions such as those advocated by Fletcher (1949) is also open to doubt, since every patient is an individual problem, and whatever may be understood by the term 'ulcer diathesis', it must be recognized that the patient should be studied and treated as a whole, his ulcer being regarded merely as an incident in the natural history of the disease; or, as Jordan (1941) expressed it, 'the life history of ulcer can be said to end only with the life of the patient'. A leading article in the *British Medical Journal* (1943) states that: 'to separate the ulcer patient from his diathesis is like severing the fisherman from his soul, and until we learn some new secret of Nature we must be content to try to teach the patient how best to live at peace with his ulcer—and to do this he must probably learn how to live at peace with himself'.

If the world as a whole were to attain this ideal state, peptic ulcer might no longer be a problem to the medical profession. In these days of changing fashions in medicine and surgery it is perhaps too early to say whether the separation of the patient from his stomach can offer more than a temporary solution to the problem.

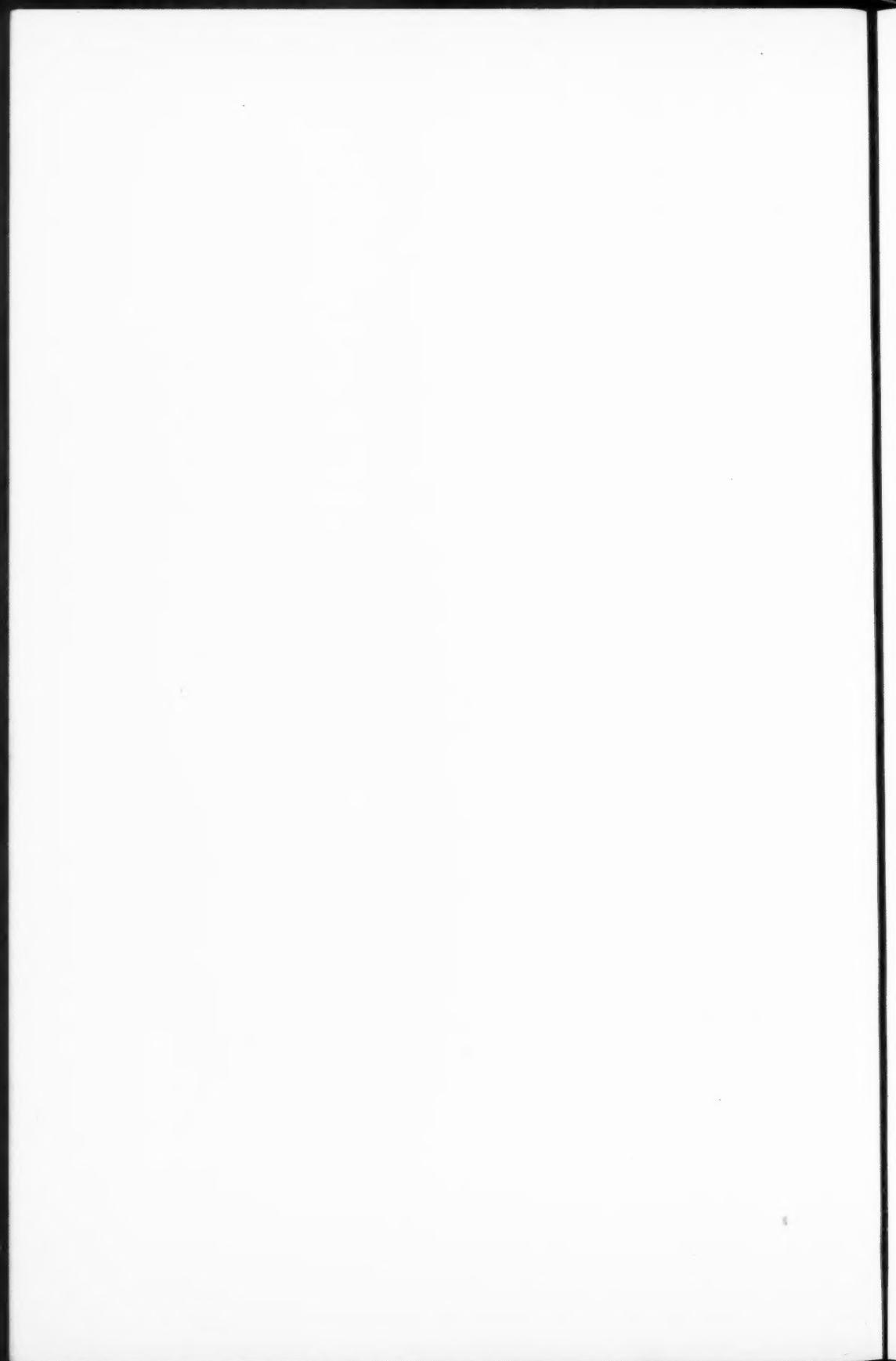
We are indebted to the Medical Director-General of the Navy for permission to publish this paper; to Surgeon Vice-Admirals Sir Sheldon F. Dudley and Sir Henry St. C. Colson, who were responsible for promoting the experiment; to Surgeon Lieutenant-Commander C. A. Grant, R.N.V.R., and Surgeon-Commander (now Surgeon-Captain) W. R. S. Panckridge, R.N., who carried out the radiological examinations; and to the Director-General of Medical Services, Ministry of Pensions, for assistance in tracing the patients. We also wish to record the practical and helpful interest in the scheme which was taken by the late Admiral Sir Max K. Horton in the midst of his heavy responsibilities as Commander-in-Chief, Western Approaches.

Summary and Conclusions

1. An experimental scheme for the rehabilitation and employment of men suffering from peptic ulcer was established in the Royal Navy during the Second World War. Only proved cases were chosen, and all the subjects were highly skilled and willing to continue serving. Employment on shore and harbour duties was provided, and suitable arrangements were made for dieting and medical supervision.
2. Sixty-three men were under observation for over 12 months. At the end of this period approximately half had radiological signs of active ulceration, although three-quarters were free from symptoms.
3. A similar proportion suffered during the year from a relapse of symptoms necessitating time off work, but in half the cases this was for a week or less.
4. Attention is drawn to a group of patients who have frequent or constant minor dyspepsia. Abnormal personality-traits are common in this group, and the presence of an active ulcer may be overlooked if psychoneurotic features are conspicuous.
5. A follow-up study conducted five years later showed that in half of the original number of patients time was being lost off work for more than a week each year on account of dyspepsia. Only four of the 52 patients who were traced had remained completely free from symptoms. In most of the patients the attention still paid to careful dietetic habits seemed to be determined by the frequency and severity of the periodic recurrences of symptoms.
6. It is concluded that in this series of patients the natural history of the disease was not materially influenced by the prolonged medical treatment.

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SYSTEMIC LUPUS ERYTHEMATOSUS¹

A Clinical and Pathological Study

By STEPHEN C. GOLD AND N. F. C. GOWING

(From the Departments of Dermatology and Pathology,
St. George's Hospital, London)

With Plates 30 to 33

THE characteristic syndrome of widespread erythematous rashes associated with high fever, arthritis, and urinary abnormalities, most frequently occurring in young women, is widely known as systemic lupus erythematosus. During the past four years we have observed 26 cases, some of which have been typical examples, while others, being less florid, have posed a greater diagnostic problem. In view of the considerable frequency with which this condition has been discussed in the American and continental literature it is surprising that only short accounts have been published in this country (Roxburgh, 1933; Beare, 1949; Fergusson, Milne, and Shand, 1949).

History. Kaposi, in a brief report in 1859 and later in detail (Kaposi, 1872), described an acute form of lupus erythematosus. His 11 patients, nine of whom were female, suffered from a violent and fatal illness, but he realized that this disease could develop from chronic discoid lupus erythematosus or could arise *de novo*. He recognized many of the systemic symptoms, and paid particular attention to the varying cutaneous manifestations. With Hebra (1875) he added to his original observations, and pointed out that a fatal outcome was invariable in the acute form and ultimately probable in the subacute variety. The first mention of an acute case occurring in this country was made by Fagge and Pye-Smith (1891). Though never recorded in the literature, a detailed autopsy report has been discovered in the pathological records of St. George's Hospital, London. Pernet (1908) in his *Thèse de Paris* considered a new type, 'le lupus erythémateux aigu d'emblée'. After the reports of Boeck (1898 *a, b*) many papers appeared incriminating tuberculosis as the cause (Sequeira and Balean, 1902; Friedlander, 1911) though other observers were more sceptical (Koch, 1896; Jadassohn, 1904; Mook, Weiss, and Bromberg, 1931; Keil, 1933). Attribution of the disease to streptococcal infections (Barber, 1915, 1920, 1938, 1941 *a, b*) caused surprise, but such a thesis was supported by the findings of others (Sundt, 1926; Madden, 1932; Hopkins, 1935; Adamson, 1947; Ayvazian and Badger, 1948). A clinical appraisal from the broader view of general medicine, rather than that of dermatology alone, suggested that the unusual combination of symptoms occurred in

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so characteristic a manner that the process was a definite clinical entity (Goeckerman, 1923; Keefer and Felty, 1924).

Classification. Many attempts have been made at classification, particularly with a view to indicating the relationship of the chronic discoid form to the various systemic types of the disease (Keil, 1937a; Urbach and Thomas, 1939; Selzer, 1945; Lian, Siguier, and Sarrazin, 1947). The most useful method is to separate the purely cutaneous disease from the systemic variety. The cutaneous types may be localized (chronic, discoid) or disseminated; the systemic types may be subacute or acute, depending on the tempo of the process. But the more thoroughly cases are investigated, the more often is systemic involvement revealed. Thus an increased erythrocyte sedimentation rate, anaemia, leucopenia, and hyperglobulinaemia are evident in cases which clinically are of the purely cutaneous type, and are strong evidence of the pathological unity of the two processes (Montgomery and McCreight, 1949).

Frequency. The great rarity of the condition has been stressed (Schmidt, 1914; Delzant, 1945), but we believe it to occur more commonly than is generally supposed. There may be an increase in incidence, but it is probable that a wider appreciation of the multiform clinical picture accounts for more frequent reports at the present time (Engman, 1937).

Sex distribution. Twelve of our 14 patients who had the acute type of the disease, and all 12 who had the subacute form, were female. This is in accord with other observations, in which the percentage of female patients varies from 77 to 95 (Kierland, 1940; Baehr, 1944). Reports of male sufferers are uncommon (Gibson, 1925; White, 1926; Davis and Ayman, 1927; Snapper, 1935).

Age distribution. Most of our patients were between 20 and 40 years old, and it has been suggested that the period of sexual activity is a predisposing factor (Baehr, Klemperer, and Schifrin, 1935a). Montgomery and McCreight (1949) found the average age at onset of the acute disease to be 21 years, and of the subacute disease 30 years, figures which are in close agreement with our own. In the few juvenile cases reported it seems that, as opposed to adults, the female do not outnumber the male patients.

Pre-existing discoid lupus erythematosus. In three (21 per cent.) of our 14 acute cases and seven (58 per cent.) of our 12 subacute cases, the patients had suffered earlier from the discoid form of the disease; Montgomery (1939, 1940) found that a third both of the acute and of the subacute cases had previously presented evidence of the chronic disease. This association of the two types has been apparent from Kaposi's earliest observations (Jadassohn, 1904; Roxburgh, 1933; Martin and Larrotcha, 1950). It should be noted that on laboratory investigation widespread variations from the normal are frequently found in patients with the cutaneous form of the disease. Disturbances of the serum-protein distribution, peripheral blood-flow, and capillary permeability all indicate that vascular and other abnormalities are widespread in this localized disease (Herrmann and Kanof, 1947; Walker and Benditt, 1950; Huff, Taylor, and Keys, 1950). It has been suggested that the chronic discoid form represents the cutaneous manifestation of a systemic abnormality held in check, and

that once the restraining force is released the generalized disease becomes manifest (Goldman, 1951).

Precipitating factors. The systemic illness may be precipitated, in patients who have the chronic disease, by a variety of drugs and physical agents. Gold and the sulphonamides have a bad record in this respect, but iodine, thiourea, and mepacrine have occasionally been to blame. Of physical agents, the effect of sunburn has long been recognized as a disseminating factor (Bunim, 1940; Keil, 1940; Kierland, 1940), and occasionally it may initiate the disease (Bechet, 1932; Denzer and Blumenthal, 1937). Injections of tuberculin and horse serum, insect bites, burns, and irradiation of the skin by X-rays have at times been incriminated (Ravagli, 1915; Cluxton and Krause, 1943; Fox, 1943).

Course. Acute systemic cases often start suddenly as a sequel to some obvious event, such as sunburn or a reaction to drugs. Their course is violent, and death often occurs within a few weeks. Subacute forms may reveal exacerbations and remissions for many years, ultimately to prove fatal during an acute phase. If the first abnormal signs do not include a characteristic rash, the condition often masquerades as rheumatic fever, rheumatoid arthritis, nephritis, or endocarditis. It is usual to find that patients have noticed loss of weight, lassitude, and poor tolerance to exertion for many months before any specific symptom has developed. The occurrence of chilblains or 'Raynaud-like' attacks is common; thrombocytopenic purpura and haemolytic anaemia are rarely associated with systemic lupus erythematosus.

Signs and Symptoms

Cutaneous. In the systemic variety one of two processes may have occurred: generalization may have developed from previous discoid disease, in which case typical atrophic, scaly patches will be seen in association with all degrees of the changes about to be described; alternatively, and more commonly, the systemic disease may develop spontaneously. The rashes are often nondescript, though occasionally it is possible to make a diagnosis on their appearance alone. The face is particularly liable to be involved, especially the cheeks and bridge of the nose; most patients at some time or another demonstrate this erythema, but it is important to emphasize the fact that facial flushing may be seen in a variety of febrile conditions and, in the absence of substantiating clinical signs, is insufficient evidence for the diagnosis of lupus erythematosus. The rash may be in the form of erythematous patches, often impalpable, which tend to become confluent; though commonly seen on the cheeks and nose, they may occur on other parts of the face, such as the ears, lips, and superciliary prominences, and on a V-shaped area of the neck and chest. It is unusual to see much scaling, and the colour may vary from pink, through red, to a livid cyanotic tint. The skin often becomes oedematous, so that papular, vesicular, or even bullous lesions may result; when bullae rupture, crusted and raw surfaces develop, but it is unusual for deep ulceration to occur. Occasionally bullae may be widespread (Bulkley, 1906; Dawson, 1907; Davis and Ayman, 1927; Gray, 1931-2; Gold, 1951). Erythema localized round the nail folds, and often associated with a

glassy appearance of the skin, is well recognized. When viewed with a capillary microscope the area reveals an increased number of widely dilated arterioles (Baehr, Klemperer, and Schifrin, 1935a); this periungual erythema, also seen in dermatomyositis and acrosclerosis, may proceed to telangiectasia. Widespread telangiectasia does not always denote chronicity (Robertson and Klauder, 1923). Erythematous macules, often seen on the palmar surface of the hands and fingers, are usually small and painless; they are particularly common on the thenar and hypothenar eminences. Painful nodules, which disappear in a few days, are frequently present, situated deeply in the dermis; they may be skin-coloured or pink, and are often found on the hands, arms, and feet (Duperrat, 1947); they have been likened to the 'nodosités cutanées éphémères' of the French (Osler's nodes). During an acute phase it is not unusual to see non-descript erythema developing at sites of trauma such as the elbows, knees, and buttocks, and at times the skin lesions may imitate those of acute pellagra, erythema multiforme, or erysipelas (Scholtz, 1922; Weidman and Gilman, 1931). A characteristic but infrequent type of rash is the 'erysipelas perstans faciei' of Kaposi. It is deeply erythematous, with marked oedema, and usually occurs on the face; it differs from true erysipelas in its slower extension and its livid hue. 'White-centred petechiae' figure extensively in the early descriptions, authors stressing the fact that the white centres should not be raised—a point of difference from those seen in staphylococcal septicaemia.

Two of our patients developed thrombocytopenic purpura before the lupus became evident. In one a marked improvement in the haemorrhagic element was produced by splenectomy. This association is well known, and a reduction of circulating platelets may be correlated with the development of purpura (Sequeira, 1920; Lyon, 1933; Templeton, 1934; Keil, 1937b; Brady and Neal, 1948). Purpuric eruptions occurring without a coexistent thrombocytopenia are often localized around the fingers and toes, characteristically under the free edge of the nail. Such lesions signify localized vascular thrombosis or rupture of small vessels. Small petechial haemorrhages are common, but 'splinter' haemorrhages in the nails are not. At the height of the disease erythematous or petechial lesions may develop on the mucous membranes of the mouth; they soon proceed to shallow ulceration surrounded by a red or haemorrhagic areola, and tend to heal readily as the general condition improves. The vulva and vagina may be similarly involved (Madden, 1932). Alopecia is common (Belote, 1939), and when present is diffuse and secondary to the toxæmia; it is not to be confused with the cicatricial type seen in the chronic discoid disease.

It thus becomes apparent that the cutaneous manifestations are polymorphic, a wide variety of rashes occurring simultaneously or in succession. We have witnessed most of the cutaneous changes that have been described above, but would not put great stress on morphological minutiae. Furthermore we do not believe that an atypical rash precludes a diagnosis of lupus erythematosus, and are prepared to accept virtually any type of inflammatory skin change as a possible accompaniment.

Arthritic. Joint symptoms play a prominent part in the clinical syndrome, for

nine out of 14 patients (64 per cent.) of our 'acute' group suffered active arthritis at some time. Of the 'subacute' group fewer had severe joint symptoms (17.5 per cent.). Slocumb (1940) found that joint pains were noticed in 20 per cent. of chronic, 57 per cent. of subacute systemic, and 63 per cent. of acute cases. The arthritis is acute in type, often subsiding rapidly; its association with peri-arthritis, synovitis, and fibrositis may make differentiation from rheumatic fever difficult. Should symptoms persist for many months, a residual arthritis resembling the subacute infective form may remain. It is unusual to see radiographic changes, and permanent joint deformity is rare (Tumulty and Harvey, 1949). Articular symptoms may last from six months to as many years, and rheumatoid arthritis may be closely mimicked.

Muscular. We have observed swelling and tenderness of muscles (Case B), as did Keefer and Felty (1924). The resemblance to dermatomyositis may be notable, and clinical differentiation may occasionally be impossible (Keil, 1940).

Renal. In only one patient (J) of this series were symptoms primarily referable to renal involvement. Her urine showed a gradually increasing amount of albumin and casts, while her blood-pressure mounted. In the terminal stages she was grossly oedematous, hypertensive, and uraemic. The development of such a 'nephrotic' syndrome is uncommon (Brenner, Leff, and Hochstein, 1948; Daugherty and Bagginstoss, 1950). Abnormal urinary findings and post-mortem evidence of nephritis have been recognized since Brooke (1895) first drew attention to them. Symptoms due to renal involvement are not common, though the urine frequently contains albumin and casts. According to Keith (1940) renal failure plays little part in causing death, though with Stickney (Stickney and Keith, 1940) he noted that four of their 13 patients died in uraemia.

Gastro-intestinal. Several of our patients had suffered recurrent attacks of diarrhoea and vomiting, but the findings in one patient (C) were particularly striking. This woman had a long history of dyspepsia, and radiologically her stomach revealed an unusual filling defect; on gastroscopy an oedematous, eroded, and haemorrhagic area presented an uncommon appearance. Diarrhoea is the commonest gastro-intestinal symptom (Stillians, 1942), and Stickney (1940) noticed a clinical resemblance to typhoid fever. Sometimes the association of abdominal pain and vomiting may simulate acute abdominal disease (Downing and Messina, 1942; Moxon, 1948; Vallat, Roux, and Leobard, 1949), and melaena occasionally occurs (Goldstein, 1947), so that when these patients come under surgical jurisdiction it may be with difficulty that the surgeon's hand is stayed. Ulceration of the oesophagus (Rathe and Shaw, 1943) and even necrosis of large areas of gut wall (Garfield, Steele, and Houghton, 1934) may be seen.

Serous. Eight of our patients (31 per cent.) developed pleural, and two (8 per cent.) pericardial effusions. Such effusions are generally absorbed, though occasionally a condition resembling obliterative polyserositis may result. We observed ascites in only one patient (J), in whom it was part of a nephrotic syndrome. Stickney (1940) suggested that many obscure cases of polyserositis may in reality be systemic lupus erythematosus.

Cardiac. The tachycardia, cardiac arrhythmias, and murmurs which occur are compatible with any prostrating illness. It is impossible to be certain of the development of verrucous endocarditis during life, and cardiac failure except as a terminal event is not usual. The development of mitral stenosis (Case Y) has not to our knowledge been reported before, but we believe that it is not inconsistent with our views on the pathogenesis of lupus erythematosus. Cardiac dilatation may occasionally be observed, and pericardial effusions are well recognized. Other observers agree on this lack of specificity of cardiac symptoms and signs (Lian, Siguier, Duperrat, and Sarrazin, 1947; Humphreys, 1948; Rivet, 1948). It is not surprising that the electrocardiographic findings are also non-specific. In seven (27 per cent.) of our patients the reports described inversion of T waves, low voltage, and defective S₂ and S₃. These findings are in accordance with the essential variability of myocardial damage described by others (Contatto and Levine, 1939; Liebow and Feil, 1947).

Glandular. Widespread enlargement of lymphatic glands was a feature of four of our patients (E and U, in whom there was splenomegaly; Z, a woman of 43 years, whose cervical glands suppurated, and M, one of the two male patients). The glands were tender on pressure. Many other patients revealed minor degrees of lymphadenopathy from time to time. Attention was drawn to this finding by Schaumann and Introzzi (1931); Fox and Rosahn (1943) analysed 277 cases, and estimated that some lymphatic glandular enlargement is present in more than 65 per cent. of patients. Stillians (1942) suggested that such a finding indicated chronicity. The glands generally are discrete and soft, may vary in size up to 5 cm. diameter and, though often tender, never break down. Clinical enlargement of the spleen is uncommon, though it seems more frequent in the young, as in Still's disease. Enlargement of the spleen was detected in only nine (34·6 per cent.) of our patients, but it is possible that minor degrees may have been missed by infrequent examination. Several reports of splenomegaly are available (Fullerbaum, 1926; Rose and Goldberg, 1935); Kaiser (1942), reviewing its frequency, found that a third of the patients showed no splenic enlargement, while in the remaining two-thirds it was only slight but quite definite. Enlargement of the liver is not a common finding, and occurred in only one (4 per cent.) of our patients. Matthews (1942) stated that it may develop as a result of cloudy swelling, pylephritis, or abscess formation. Tumulty and Harvey (1949), in their analysis of 32 patients, found liver enlargement frequent, and ascribed it to deposition of fat. Some of their patients showed disturbance of liver function as revealed by standard tests.

Nervous. Three of our patients suffered epileptiform fits, which in two of them were a predominating feature. The high incidence of such attacks is widely acknowledged (Klempner, Pollack, and Baehr, 1941; Tumulty and Harvey, 1949; Haserick, 1951; Russell, Haserick, and Zucker, 1951). Focal vascular lesions in the central nervous system, especially thrombotic cerebral episodes, which are more common in the thrombocytopenic states, are occasionally seen. Acute aseptic meningitis, encephalomyelitis, peripheral neuritis, and a variety of neurological syndromes rarely occur (Jarcho, 1936; Fisher, 1939;

Keil, 1940; Pollak and Ziskind, 1943; Daly, 1945; Sedgwick and Von Hagen, 1948; Heptinstall and Sowry, 1952).

Ophthalmic. The discoid disease may occasionally involve the lid margins, which become atrophic. Conjunctivitis as it occurred in our patient M was of a violaceous tinge, as noted by Klauder and DeLong (1932), and would fluctuate with his other symptoms of arthritis and urticaria. In only three patients (B, J, and V) were retinal lesions discovered, and the blurred disk margins, central exudate, and venous congestion were comparable with the observations of other authors (Semon and Wolff, 1933; Wagener, 1946). Baehr, Klemperer, and Schifrin (1935 a) reported fundus changes in 50 per cent. of their patients, and other writers have stressed the frequency and importance of such findings (Keil, 1940; Tumulty and Harvey, 1949). According to Cordes and Aiken (1947) no single fundus lesion or combination of such lesions is diagnostic, but they noticed that early signs of systematization were dilatation of the retinal vessels and the subsequent appearance of 'cotton-wool' patches. They described these changes as hypertensive in type, secondary to renal involvement, though in fact hypertension is not common. Maumenee (1940) recorded his findings as cytoid bodies, haemorrhages, and papilloedema. The retinal changes, evanescent in character, are a manifestation of widespread vascular injury, and sharply distinguish lupus erythematosus from rheumatic fever and rheumatoid arthritis.

Clinical Pathology

Blood changes. Many observers have drawn attention to changes in the blood, and MacLeod (1908) stressed the frequency of hypochromic anaemia. All the cellular elements may be depressed, and an important diagnostic feature is leucopenia, particularly of granulocytes, producing a relative monocytosis (Stickney, 1940). Leucocytosis, in the absence of accompanying infection, is regarded as strong evidence against the diagnosis, though Bunim (1940) reported it in one case in which the diagnosis was justified. Leucopenia has been a constant feature of all our cases; sometimes it has been striking (less than 2,000 leucocytes per c. mm.)—but generally it has been moderate (3,000 to 4,000 leucocytes per c. mm.). During active infection the white blood-cell count never exceeded 10,000 per c. mm. The degree of leucopenia may well be correlated with the degree of L.E.-cell production, and we have observed a leucocytosis following the administration of cortisone. The white cells may be of immature type, and on rare occasions have resembled leukaemic cells; the descriptive term 'leukemoid' has been used (Hollander, Kastlin, Fisher, and Schlesinger, 1932). Such immaturity of cells, especially if accompanied by splenomegaly and adenopathy, may simulate a primary blood dyscrasia. We have occasionally noticed eosinophilia, and a constant figure of more than 8 per cent. has been recorded (Vallat, Roux, and Leobardy, 1949). The erythrocyte sedimentation rate is generally increased, but this change may be associated with the abnormal distribution of serum-proteins. The occasional observation of a normal erythrocyte sedimentation rate when the patient is critically ill has, in our

experience, been associated with the presence of cold agglutinins, and occurred in two of our patients. The ability to develop multiple antibodies to transfused blood has been an intriguing feature. Baldwin (1945) reported a Rh-negative patient, transfused with Rh-positive blood, who developed Rh antibodies and died as a result; another patient (Callender, Race, and Paykoç, 1945; Callender and Race, 1946) developed five separate red-cell antibodies after multiple transfusions. A man suffering from an undiagnosed collagen disease developed six separate antibodies (Waller and Race, 1951). Thrombocytopenic purpura is occasionally found, and two of our patients were so diagnosed several years before lupus erythematosus became apparent. Though the tendency to thrombocytopenia improved without splenectomy in one patient (G), a male patient (V) had his spleen removed with great benefit. Subsequently these patients showed a tendency to develop purpuric lesions which coincided with a reduction of platelets (Rose and Goldberg, 1935; Keil, 1937*b*; Brady and Neal, 1948).

The Coombs test was performed by Zoutendyk and Gear (1950); it was found directly positive in one patient with the systemic disease, and they also noted a positive result in the blood of a sufferer from discoid lupus erythematosus. They have subsequently enlarged their concept of autosensitization of red cells in this disease (Marshall, Zoutendyk, and Gear, 1951; Zoutendyk and Gear 1951), and these results have been confirmed by one of us (Gold, 1952*a*) who drew attention to the fact that cold agglutinins also are frequently found in cases of the systemic type, and that during acute episodes the degree of cold agglutination may be so great as to interfere with blood investigations. We found that seven (27 per cent.) of our patients revealed abnormal cold agglutination, and eight (31 per cent.) showed a positive Coombs test. Over a period of observation both these reactions were found to vary in titre, and could disappear and return later. One patient (Y) developed a haemolytic anaemia, for which splenectomy was performed some years before the diagnosis of lupus erythematosus was made. She showed a positive Coombs test, marked cold agglutination, and strong Wassermann and Kahn reactions, though the degree of all these phenomena would vary. A factor present in patients' serum which would agglutinate sheep's red cells, previously sensitized by the addition of anti-sheep's-red-cell-serum from the rabbit, has been demonstrated in other series, and in our patient (Z), as well as in patients suffering from rheumatoid arthritis, in whom it seems regularly to be present (Rose, Ragan, Pearce, and Lipman, 1948; Ball, 1950).

The L.E. cell. Hargraves in 1946, and later in association with Richmond and Morton (1948), described unusual cells in the bone-marrow of patients suffering from systemic lupus erythematosus. They were studying heparinized specimens as a routine, and the cells which attracted their attention were of the granulocyte series; the 'L.E. cell' had engulfed one or more masses of homogeneous basophilic material, so that the cell nucleus was pushed to the periphery, giving a horseshoe or target appearance. Another cell which they described, the 'tart' cell, was usually a histiocyte with one or two secondary nuclei; this form has been found in several other conditions, and is not regarded

as specific. They made no claims as to the specificity of the L.E. cell phenomenon, but mentioned that it appeared frequently during acute episodes. Many workers were sceptical of this finding, regarding it as related to heparinization and much centrifuging, but in the same year Haserick and Sundberg (1948) confirmed it in four out of five patients. Later two further features were revealed: Sundberg and Lick (1949) demonstrated that similar cells could be found in patients' peripheral blood, though not in such profusion as in the bone-marrow, while Haserick and Bortz (1949), and later Hamburger (1950), showed that the addition of plasma from a patient with lupus erythematosus to heparinized normal bone-marrow would also produce the L.E. cell. They noticed that boiling the plasma destroyed its ability to form the cell. More recently it has been shown that this phenomenon can occur in the absence of anti-coagulants (Barnes, Moffatt, and Weiss, 1950; Gonyea, Kallsen, and Marlow, 1950), and several different techniques have been described for its production. According to Moyer and Fisher (1950) three factors are probably needed for the production of the L.E. cell: active neutrophils, free nucleoprotein, and the 'factor' in the lupus erythematosus plasma. It has been shown that the ingested material takes up Feulgen's stain, and is of nuclear origin. Moyer and Fisher further proved that the material did not contain glycogen, lipids, or either acid or alkaline phosphatase, and suggested that it was of lymphocytic origin. Lee, Michael, and Vural (1950, 1951) considered the basophilic material to be autolytic products of degenerating polymorphonuclear cells, and Wiener (1950) suggested that it might be red cells sensitized (coated with auto-antibody) before phagocytosis. That the 'factor' resides in the γ -globulin fraction was shown by Haserick, Lewis, and Bortz (1950); it may disappear during remissions. Haserick (1950) was able to demonstrate the L.E. cell phenomenon in 23 out of 25 patients, and agreed that it may fluctuate in degree; he showed that the 'factor' is destroyed by heating to 65° C., but persists for longer than six months if kept cold. It is not found in other collagen diseases, but has been revealed rarely in myelomatosis and leukaemias. An experiment by Haserick and Lewis (1950) showed that rabbits can produce an antibody to the specific 'factor' and that the 'factor' is an immunologically distinct component of the γ -globulin.

Weiss (1950) described two additional features to be seen when such preparations are made: the frequent clumping together of phagocytes, and masses of the basophilic material lying free ('L.E. bodies' not yet ingested). 'Oval inclusion bodies' in the nuclear portion of the leucocyte were thought to be an early stage in the development of the L.E. body (Barnes, Moffatt, Lane, and Weiss, 1950). These workers advocated the use of the patient's peripheral blood mixed with healthy peripheral blood as the simplest technique, and it is this method, and the one described by Mathis (1951), that we have used. In this country Holman (1951) recorded L.E. cells in three patients, and Smith (1952) regarded the test as remarkably specific, though he noted reports of occasional typical cases in whom the test was negative. It has been suggested by one of us (Gold, 1952*b*) that the phenomenon may be a counterpart of

red-cell sensitization, and is in fact another form of auto-sensitization, though it must be appreciated that the L.E. cells are an *in vitro* finding, and are not seen as such *in vivo*. In the present series L.E. cells were found in six of 15 patients (40 per cent.) in whom the examination was carried out. In one patient, who died during an acute phase, they were never demonstrated in spite of repeated attempts.

Serum-proteins. Reversal of the usual albumin/globulin ratio occurred in all our patients at one time or another, and we feel that hyperglobulinaemia is such a fundamental anomaly that the diagnosis should be suspect if it is absent. This hyperglobulinaemia is often associated with a depletion of serum-albumin (Coburn and Moore, 1943; Thyresson, 1944). The excess of globulin is largely made up of the γ -fraction, and this fraction may be responsible for the high erythrocyte sedimentation rate. While all clinical manifestations may be reversible, an inversion of the usual albumin/globulin ratio will follow and not precede any exacerbation of symptoms. Borrie (1951) demonstrated an undue tolerance to injected heparin. Whereas blood-clotting time is usually prolonged after intravenous injection of heparin, these patients appear readily to neutralize this effect. Heparin is a mucitin polysulphuric acid, having a structure similar to hyaluronic and chondroitin-sulphuric acids; Borrie therefore suggested that the neutralizing agent was probably an abnormal globulin.

Positive serological reactions. For some years it has been noticed that the sera from patients with lupus erythematosus may give positive results to the Wassermann, Kahn, and other serological tests used for the detection of syphilis. Such a finding was in the first place attributed to the coexistence of two diseases, but Davis and Ayman (1927), reporting two male patients, suspected that it did not indicate syphilitic infection. Subsequent observers have reported similar findings (Gitlow and Goldmark, 1939; Sompayrac and Hailey, 1944; Pillow and Palmer, 1945). Montgomery (1940) found that 17 per cent. of his patients gave positive reactions, and most authorities have come to accept such a finding as not unusual (Baehr, 1947). Both Wassermann and Kahn reactions were positive in only two patients of the present series (K and Y), and both these patients also showed a high degree of cold auto-agglutination. Rein and Kosztant (1950), analysing the findings in 178 patients, found positive results in 35 per cent., though in most cases the reactions were of low titre. Coburn and Moore (1943) showed that the γ -globulin from lupus patients is both quantitatively and qualitatively distinct from syphilitic antibody, the latter being destroyed by heating to 62° C. for five minutes. In electrophoretic studies of serum from syphilitic patients, normal subjects, and patients presenting biological false positive reactions, it is apparent that the syphilitic patients show an increase in the α_1 - and γ -globulins, while the α_2 - and β -fractions are normal (Cooper, Craig, and Beard, 1946). In subjects presenting false positive reactions the γ -fraction is raised.

Urinary findings. Krupp (1943) reviewed the urinary findings in 21 patients (some of whom had polyarteritis nodosa) and found abnormal urine in 66 per cent. He felt that the 'unique' composition of the urinary sediment, comprising

red cells, oval fat-bodies, fatty casts, blood casts, and protein, occurred in no other condition. More recently Miale (1947), reporting three cases, confirmed the fact that white and red blood-cells occur in the urine frequently, and that casts, which may be hyaline or waxy, and sometimes vacuolated, are common. The degree of albuminuria is variable, and since all these changes may fluctuate we feel it is necessary that the urine should be repeatedly examined, but we do not believe there is anything unique about the deposit. It has been stated that the urinary excretion of 17-ketosteroids is low, while creatinuria is abnormal, providing evidence of a 'disturbed ovarian function' (Lamb, Lain, Keaty, and Hellbaum, 1948). It is difficult to attribute these findings to any specific aspect of the disease.

Patients Investigated

Our 26 patients fall roughly into two groups, the acute (14 cases) and the subacute (12 cases); such a division is not clear-cut, as some patients may

TABLE I
Systemic Lupus Erythematosus: Symptoms

Patient	Sex	Age at onset (years)	Clinical type	Presence of rash	Pre-existing discoid L.E.	Fever	Joint symptoms	Splenomegaly	Adenopathy	Eye symptoms	Fundus lesions	Nervous symptoms	Gastro-intestinal symptoms	Diffuse alopecia	Drug sensitivity	Rosenthal-type symptoms	Present state
A	F	30	Chronic discoid → Acute	+	+	+	-	-	-	-	-	-	-	-	-	-	Dead
B	F	37	Chronic discoid	+	+	+	+	-	-	+	+	-	-	+	+	+	Dead
C	F	57	Acute	+	-	+	+	-	-	-	-	-	-	-	-	-	Dead
D	F	62	Subacute	+	+	+	+	+	+	-	-	-	-	-	-	-	Remission
E	F	7	Acute	+	-	+	+	+	+	-	-	-	-	-	-	-	Dead
F	F	25	Subacute	+	-	+	+	-	-	-	-	-	-	-	-	-	Remission
G	F	24	Subacute → Acute	+	-	+	+	+	+	-	-	-	-	-	-	-	Dead
H	F	33	Subacute → Acute	+	-	+	+	-	+	-	-	-	-	-	-	-	Dead
I	F	24	Acute	+	-	+	+	-	+	-	-	-	-	-	-	-	Dead
J	F	30	Acute	+	-	Intermittent	+	+	-	-	-	-	-	-	-	-	Dead
K	F	33	Acute	+	-	Intermittent	+	+	-	-	-	-	-	-	-	-	Dead
L	F	25	Acute → Subacute	+	-	Intermittent	+	+	+	-	-	-	-	-	-	-	Progressive polyserositis
M	M	38	Acute	+	+	+	+	-	+	-	-	-	-	-	-	-	Remission
N	F	29	Subacute	+	+	-	+	-	-	-	-	-	-	-	-	-	?
O	F	38	Acute	+	-	+	+	-	+	-	-	-	-	-	-	-	?
P	F	22	Subacute	+	-	+	+	-	+	-	-	-	-	-	-	-	Remission
Q	F	34	Subacute	+	-	+	+	-	+	-	-	-	-	-	-	-	Remission
R	F	22	Subacute	+	+	+	+	-	-	-	-	-	-	-	-	-	Remission
S	F	26	Subacute	+	+	+	+	-	-	-	-	-	-	-	-	-	Remission
T	F	21	Subacute	+	-	+	+	-	-	-	-	-	-	-	-	-	Remission
U	F	47	Subacute → Acute	+	-	+	+	-	-	-	-	-	-	-	-	-	Dead
V	M	28	Subacute	+	-	+	+	+	+	-	-	-	-	-	-	-	Subacute activity
W	F	22	Subacute	+	+	Intermittent	+	-	+	-	-	-	-	-	-	-	Subacute activity
X	F	18	Subacute	+	+	Intermittent	+	+	+	-	-	-	-	-	-	-	Subacute activity
Y	F	28	Subacute	+	-	Intermittent	+	+	†	-	-	-	-	-	-	-	Dead
Z	F	43	Subacute	+	-	Intermittent	+	+	+	-	-	-	-	-	-	-	Remission

* Spleen removed in 1941 for thrombocytopenic purpura.

† Haemolytic anaemia in 1948.

exhibit acute episodes and then return to subacute activity. One patient (F) appears to have made a prolonged and complete remission; all the others who are still alive show some signs of activity. The cases are presented in tabular

TABLE II
Systemic Lupus Erythematosus: Aetiology

Patient	Sex	Age at onset (years)	Presenting symptoms		Systems predominantly involved	Previous infections	Precipitating factors or possible aggravators	Previous sulphonamides
			Previous typical disease	L.E.				
A	F	30	Rash	+	Cutaneous	Chronic sepsis	?Sulphonamides	+++
B	F	37	Rash	+	Pulmonary	Chronic sepsis	Oophorectomy	+++
Acute	C	57	Gastric Pains	-	Joint	Adenitis	?Sulphonamides	+ -
	E	7	Gastric Pains	-	Gastric Joint	Peritonitis	?	++
	G	24	Rash	-	Vascular	Scarlet fever	?	+
	H	33	Rash	-	Cutaneous	Thrombopenia	Sunburn	-
	I	24	Arthritis	-	Cutaneous	Tonsillitis	?	+
	J	30	(X-ray of lungs)	-	Joint	Cystitis	Tuberculous salpingitis	-
	K	33	Rash	-	Renal	Scarlet fever	?Oophorectomy	++
	L	25	Arthritis	-	Cutaneous Joint	Styes	Gold	-
	M	38	Rash	+	Joint	Sinusitis	?	+
	O	38	Arthritis	-	Pleural	Fibroid pulmonary tuberculosis	?	Not known
	U	47	Rash	-	Joint	Recurrent quinsy	?Sudden menopause	++
	V	28	Pneumonia Abscesses	-	Cutaneous Pulmonary Purpura Joint	Abscesses Pneumonia	Sulphonamides	++
	D	62	Rash	+	Cutaneous	Pneumonia	?Sun	+
	F	25	Rash	-	Cutaneous Renal	Chronic tonsillitis	?Sun	++
Subacute	N	29	Rash	+	Cutaneous Nervous	..	?	-
	P	22	Rash	-	Cutaneous	..	Childbirth	++
	Q	34	Rash	-	Cutaneous	Boils	Sulphonamides	+
	R	22	Rash	+	Cutaneous	Cystitis	Haemorrhagic pituitary necrosis	-
	S	26	Rash	+	Cutaneous	Exposed to open pulmonary tuberculosis	?Sensitivity to M. tuberculosis	-
	T	21	Rash	+	Cutaneous	Tuberculous glands	?	-
	W	22	Rash	+	Cutaneous (Chilblain)	Tuberculous glands	Sun	++
	X	18	Rash	+	Joint	Tuberculous glands	Sulphonamides	-
					Cutaneous Spleen Lungs	Tonsillitis	Penicillin	-
	Y	28	Arthritis	-	Joint Nervous	Cellulitis	?	-
	Z	43	Rash	-	Haemolytic anaemia Cutaneous Glands	-	Bee-stings Sulphonamides	++

form, but as an example of the multiform symptoms and the diagnostic difficulties that may be present in the subacute disease, it is worth while relating the progress of one patient, who has been observed from the outset.

Case Y. A woman of 28 years developed arthritis of the shoulders and hands in 1947. The condition was diagnosed as rheumatoid arthritis, for which she

was prescribed a course of gold injections. After the third injection a widespread scaly rash developed, necessitating a course of dimercaprol. The rash gradually improved, but a haemolytic anaemia developed of such degree that repeated transfusions were necessary to maintain life. It was found that the blood contained cold agglutinins of a high titre, the Coombs test was strongly positive, and the serum-proteins showed a reversal of the usual albumin/globulin ratio. Her spleen became palpable and, as excessive haemolysis continued, splenectomy

TABLE III

Systemic Lupus Erythematosus : Haematological Findings

Patient	Leucopenia (lowest white-cell count)	Erythrocyte sedimentation rate (mm./hr.)	Thrombo- cytopenia	L.E. cells in peripheral blood	Coombs test	Cold aggluti- nation
B	5,000	63	Not examined	Not examined	Not done	+
D	2,600	42	—	—	—	—
G	3,600	34	+	+	—	—
I	5,000	53	—	+	+	+
J	4,800	60	—	—	—	—
K	3,500	*	—	+	+	+
M	4,000	48	—	+	+	—
Q	6,000	17	—	+	+	+
R	5,000	30	—	+	+	+
T	5,900	32	—	—	—	+
U	1,400	60	—	—	+	—
V	2,900	40	—	Not examined	Not done	Not examined
W	5,000	80	+	—	+	—
Y	5,000	57	—	—	+	+
Z	4,000	40	—	—	—	—

* High degree of cold agglutination prevented accurate reading.

was performed, with immediate benefit. For the past three years she has been subject to various and transient erythematous rashes; she has also suffered several epileptiform fits. Quite recently it has become apparent that she has developed mitral stenosis, the fingers are becoming clubbed, and the liver is palpably enlarged. Serological studies reveal that the cold agglutination and the positive Coombs test have persisted, but their degree has shown remarkable variation. Furthermore the Wassermann and Kahn tests are positive, and the titre of these reactions also fluctuates. The urine occasionally contains red and white cells, but albumin has never been observed. Leucopenia has not been detected, nor have L.E. cells been found in the sternal marrow or peripheral blood, but when these searches were made the patient was not acutely ill. She has subsequently died elsewhere.

The combination of haemolytic anaemia, rheumatoid arthritis, epilepsy, drug sensitivity, enlargement of the liver, urinary abnormalities, and the presence of abnormal globulins, can only be accounted for under a single diagnosis—subacute systemic lupus erythematosus. The development of mitral stenosis is remarkable.

Morbid Anatomy

Early attempts to unify the pathology of systemic lupus erythematosus were directed chiefly to the vascular lesions, which were regarded as fundamental, and many workers believed that the various organs were implicated through

their blood-supply (Baehr, 1931; Baehr, Klemperer, and Schifrin, 1935, *a, b*; Jarcho, 1936; Keil, 1937 *a*; Rose and Pillsbury, 1939; Ginzler and Fox, 1940; Banks, 1941). The expression 'visceral angiitis' has been used by several authors to include systemic lupus erythematosus and polyarteritis nodosa (Selzer, 1945; Miale, 1947). A broader view was taken by Denzer and Blumenthal (1937), who suggested that the 'unknown toxic agent' had a more general effect on mesenchymal tissues, but it is chiefly to Klemperer, Pollack, and Baehr (1941) that we owe the present concept of a widespread alteration of fibrous connective tissue as the pathological basis of the disease. The lesion that has attracted most attention is the so-called fibrinoid degeneration of collagen fibres, a change which is also found in several other diseases. The interrelationships of the various 'collagen diseases' have been discussed by Klemperer (1947), Baehr and Pollack (1947), and Duff (1948). We do not propose to consider in detail the formation, significance, and chemical structure of fibrinoid, the nature of which has been investigated and discussed by several groups of workers (Altshuler and Angevine, 1949, 1951; Glynn and Loewi, 1952; Kellgren, Ball, Astbury, Reed, and Beighton, 1951; Consden, Glynn, and Stanier, 1952). It is, however, important to notice that other alterations, possibly of equal importance, occur in the connective tissues. The fibroblasts and histiocytes may undergo necrosis, or they may proliferate, and a further change results in the formation of the 'haematoxylin-staining bodies' first described in the cardiac valves by Gross (1932). The chemical nature of these bodies has been investigated by Klemperer, Gueft, Lee, Leuchtenberger, and Pollister (1950) and Klemperer (1950), who believed them to consist of deoxyribonucleic acid in a state of partial depolymerization. The bodies have been described in the heart (Gross, 1932, 1940), in lymph-nodes (Ginzler and Fox, 1940), in the renal glomeruli (Klemperer, Pollack, and Baehr, 1941; Rakov and Taylor, 1942) and in many other organs (Klemperer, Gueft, Lee, Leuchtenberger, and Pollister, 1950; Klemperer, 1950). We have observed them in the spleen, lymph-nodes, pericardium, and peritoneum. Recently Klemperer (1952) has stressed the importance of the nuclear degeneration that leads to the formation of the haematoxylin-staining bodies, and has suggested that the fibrinoid of systemic lupus erythematosus is a product of nucleoprotein disintegration. We may summarize the changes that occur in the connective tissues as follows:

1. Fibrinoid degeneration of collagen fibres; increase in ground substance; fragmentation and destruction of elastic fibres. Hyalinization and sclerosis.
2. Fibroblastic proliferation; new fibril production.
3. Necrosis of connective-tissue cells with nuclear pyknosis and karyorrhexis. The formation of haematoxylin-staining bodies.
4. Inflammatory cell infiltration, mainly by lymphocytes, plasma cells, and large mononuclears, secondary to the degenerative and necrotic changes.

It must be admitted that in some instances the post-mortem findings in cases of systemic lupus erythematosus are disappointing in so far as characteristic lesions are minimal. The patient's resistance to bacterial infection is greatly diminished, and lesions resulting from intercurrent infection may come to

dominate the pathological picture. Four of our seven patients who died had bronchopneumonia, one with empyema; one patient had tuberculous meningitis, and in another acute staphylococcal septicaemia was the immediate cause of death. Active pulmonary tuberculosis was found *post mortem* in Case J. Careful microscopic search, however, usually reveals one or more of the typical visceral lesions.

Skin. The skin lesions of both acute and chronic lupus erythematosus have been described in detail by Montgomery (1939, 1940). The only unusual findings that we have encountered are (1) two cases showing a striking increase of metachromatic ground-substance in the dermis, and (2) one case in which haematoxylin-staining bodies were present in the dermis beneath a bulla.

Serous membranes. Three of the four patients of Libman and Sacks (1924) had 'organizing fibrinous pericarditis'. Seventeen of the 23 patients reported by Baehr, Klemperer, and Schifrin (1935b) had involvement of the serous membranes, and 12 had pericarditis. The macroscopic and microscopic features have been described in detail by Gross (1940) and by Klemperer, Pollack, and Baehr (1941). Serositis was present in four of our fatal cases: pleurisy and perisplenitis in Case E; pericarditis, perisplenitis, and perihepatitis in Case B; perisplenitis and pericarditis in Case J; pericarditis in Case K. In most instances the lesions were a non-specific fibrinous inflammation, but in Case B there was extensive fibrinoid change in the pericardium, and haematoxylin-staining bodies were found in the areas of perihepatitis. Less extensive fibrinoid changes were present in the pericardium of Case K. The fibrinoid degeneration was associated with a marked inflammatory cell reaction; lymphocytes, plasma cells, mononuclears, and polymorphs had accumulated around the fibrinoid lesions (Plate 30, Fig. 1). Fibroblastic proliferation had resulted in marked thickening of the pericardium, fibrosis of the epicardial adipose layer, and obliteration of the sac. The appearances suggest that fibrinoid degeneration occurs repeatedly in the newly formed collagen. Teilum (1945) reported two cases of systemic lupus erythematosus in which he found miliary epithelioid-cell granulomas in the serous membranes. We have not observed comparable lesions.

Lymph-nodes. Lesions were found in five of our fatal cases: follicular and littoral-cell hyperplasia (Case E); distension of the sinusoids with mononuclear cells, plasma cells, and a few multinucleated cells and scattered haematoxylin-staining bodies (Cases H and B); and tuberculous adenitis of the mediastinal lymph-nodes (Cases I and J). Ginzler and Fox (1940) described focal necrosis and haematoxylin-staining bodies in their case of lupus erythematosus, while Guion and Adams (1943) found non-specific reactive hyperplasia in all six of their cases. Teilum (1945) reported the occurrence of epithelioid-cell granulomas. Foldes (1946) described necrotic eosinophile areas in the nodes, neutrophile- and eosinophile-cell infiltration, and the presence of multinucleated cells resembling the Sternberg-Reed giant cells of Hodgkin's disease.

Blood-vessels. Prominent vascular lesions were present in three cases (A, E, and K), and the lesions appear to be of two main types. The first type, affecting small arteries, was found in the lungs of patients A and K (Plate 30, Fig. 2) and

in the kidneys of patient E. All stages could be observed, from the early acute lesions to final scarring. In the early stages there is fibrinoid necrosis of the vessel wall with destruction of the media and elastica; the intima is often oedematous, swollen, and cellular, and the endothelial cells may be abnormally prominent. Inflammatory cell infiltration is less evident than in polyarteritis nodosa, and mononuclears usually predominate. There appears to be little tendency to thrombosis or aneurysm formation. The lesions are scattered irregularly along the vessels, and often affect only a segment of the wall. On healing they leave fibrous scars in the media, interruption of the internal elastic lamina, and fibrous thickening of the intima. The second variety of lesion was found in the vessels of many organs from our patient E. The arterioles, capillaries, and venules show endothelial proliferation and hyaline thrombus formation. The thrombi stain pink with eosin. They may plug the lumen completely, but often they contract away from part of the vessel wall and the free surface becomes covered by endothelium, leaving a crescentic lumen. In some cases the endothelial cells proliferate and invade the thrombus. These lesions are of interest in view of a possible relationship between systemic lupus erythematosus and the so-called platelet thrombus syndrome (Keil, 1937*b*; Beigelman, 1951).

Heart. Libman (1917, 1923) and Libman and Sacks (1923, 1924) reported four examples of 'a hitherto undescribed form of valvular and mural endocarditis'. Two of the patients had an eruption on the face 'which resembled acute lupus erythematosus disseminatus'. The macroscopic and microscopic features of the cardiac changes have been described in detail by Gross (1940). Lesions of this type were found in 13 of 23 cases reported by Baehr, Klemperer, and Schifrin (1935*a, b*) and in six of the 20 cases of Klemperer, Pollack, and Baehr (1941). We have observed them in only one instance (E), and the appearances in this case agreed with the descriptions of other authors. The verrucae were larger than those of rheumatic fever, and were pinkish or tawny in colour. They were present on both the mitral and tricuspid valves, and on the papillary muscles (Plate 30, Fig. 3). A few were found on the ventricular aspect of the posterior cusp of the mitral, close to the valve ring ('pocket lesions'). Most authors agree that the vegetations affect the right and left sides of the heart with equal frequency, and that the lesions may be found on all the cardiac valves, the auricular and ventricular endocardium, the papillary muscles, and the chordae tendineae. The histological changes have been described by Gross (1940) and by Klemperer, Pollack, and Baehr (1941) as fibrinoid change, degeneration of mesenchymal cells with the formation of haematoxylin-staining bodies, and inflammatory cell infiltration. Both these reports described extrusion of fibrinoid masses to form verrucae. It seems to us, however, that fibrin deposition must play an important part in the production of the vegetations. When these have formed, it is difficult to determine the relative proportions of fibrin and extruded fibrinoid. The vegetations in our case appear to consist largely of fibrin, and sections through the mural endocardium remote from gross vegetations show scattered foci of inflammatory cells with early fibrin deposition on the surface. We did not observe healed lesions, although fibrous thickening of the valves and fibrosis

of the mural plaques have been reported by Klemperer, Pollack, and Baehr (1941). Four of the cases of atypical verrucous endocarditis reported by the same authors showed bacterial implantation. We found no evidence of this in our patient E, although another patient (H) developed an independent acute bacterial endocarditis of the aortic valve cusps. Myocardial lesions were present in three of our fatal cases. Case H showed a marked excess of basophilic ground substance between the muscle fibres, a change also described by Klemperer (1948). Case E showed widely scattered foci of muscle degeneration and inflammatory cell infiltration, probably secondary to vascular damage. In Case B there was fibrinoid change in the connective-tissue stroma of the myocardium, with inflammatory cell infiltration and fibroblastic proliferation.

Lungs. Pulmonary lesions are of frequent occurrence, but are usually of non-specific character. Four of our patients who died had severe bronchopneumonia, one with empyema, and another with dense pleural adhesions forming part of a polyserositis. Our patients A and K showed striking fibrinoid changes in the walls of the pulmonary arteries. Miliary tuberculosis has been described after treatment with ACTH (Walker and Hulbert, 1952). Patient I of the present series had caseous tuberculosis of the tracheo-bronchial lymph-nodes and tuberculous meningitis; this patient had received a course of cortisone. Active pulmonary tuberculosis was found *post mortem* in Case J. An unusual type of lesion was described by Rakov and Taylor (1942). The lung tissue was firm and consolidated, and histological examination revealed disappearance of the alveolar walls, the tissue appearing as a solid inflammatory mass in which all structural detail was lost. Mononuclear cells were found to predominate. A similar finding was reported by Foldes (1946) in two cases; he suggested the term 'atelectizing pneumonitis' for this change. We failed to find comparable lesions in our series.

Liver. The liver may show several types of lesion, the majority of a non-specific nature. Focal necrosis was present in our Case H, and perihepatitis in Case B, while Cases E, H, I, and K showed considerable fatty infiltration. Previous reports speak of pylephlebitis and abscess formation (Rose and Pillsbury, 1939; Matthews, 1942), perihepatitis, focal necrosis, and angiitis (Klemperer, Pollack, and Baehr, 1941), and focal necrosis and fatty infiltration (Tumulty and Harvey, 1949).

Spleen. Moderate enlargement of the spleen, perisplenitis, and perisplenic adhesions are common. The smallest spleen in our series weighed only 45 gm. (Case A), the largest 330 gm. (Case J). Infarcts were present in one case, and perisplenitis in three. Microscopically we found the perisplenitis to show no specific features. This is in agreement with the observations of Kaiser (1942) who stated that, although the serosa covering the spleen may show typical fibrinoid degeneration, the histological features are often non-specific. In one instance we found foci of necrosis and scattered haematoxylin-staining bodies in the spleen. Arteritis was not seen, although it has been described by other workers. Ginzler and Fox (1940) described areas of necrosis, intimal thickening of the small arteries, necrosis of vessel walls, and haematoxylin-staining bodies.

The most constant histological feature is the presence of a curious form of periarterial fibrosis (Plate 31, Fig. 4). This occurs around the arteries of the Malpighian bodies and the penicillary arteries, and appears as concentric rings of hyaline collagen ('onion-skin' appearance). This type of lesion was found in 15 of 18 cases of systemic lupus erythematosus studied by Kaiser (1942), who also found it in 3·2 per cent. of 1,679 control cases. It also occurred in four of 13 cases of essential thrombocytopenic purpura. We have found it in six of our seven cases coming to autopsy. The nature and pathogenesis of the lesion is uncertain. Teilum (1948) regarded excessive globulin production as important in the development of the hyaline rings, which he supposed to represent a 'paramyloid' deposition. He found typical periarterial rings in a patient who had sulphonamide sensitivity with hyperglobulinaemia. We have seen similar lesions in sarcoidosis.

Kidneys. Renal involvement has long been recognized, and early reports spoke of 'soft, white swelling', 'nephritis', or 'glomerulo-tubular nephritis' (Brooke, 1895; Sequeira and Balean, 1902; Little, 1905; Short, 1907; MacLeod, 1908). Two of the patients of Libman and Sacks (1924) who had atypical verrucous endocarditis were stated to have acute or subacute diffuse glomerulonephritis. Baehr, Klemperer, and Schifrin (1935b) reported 23 cases, 18 of which showed glomerular changes, and in 13 cases the glomerular capillary walls showed the focal, hyaline thickenings which the authors described as the 'wire-loop' lesions. This lesion was recorded in three of the six fatal cases reported by Guion and Adams (1943), and has been further described by Klemperer, Pollack, and Baehr (1941) and by Daugherty and Baggenstoss (1950). Prominent renal changes were found in three of our seven fatal cases. Macroscopically the kidneys are often slightly enlarged and paler than normal. Inspection of the cut surface may show a pale, swollen cortex and fatty infiltration. Occasionally the surface shows petechial haemorrhages, and infarcts may be present, as in our Case E (Plate 31, Fig. 5). Microscopic examination may reveal changes in the glomeruli, blood-vessels, tubules, and interstitial tissue. The 'wire-loop' lesions were well-marked in our Cases E, H, and J. The capillary walls are thickened so that, in cross-section, they stand out as prominent loops which stain pink with the periodic-acid-Schiff technique, red in the picro-Mallory preparations, yellowish with van Gieson's stain, and blue or purple with Mallory's phosphotungstic-acid-haematoxylin (Plate 32, Fig. 6). Although these changes are very characteristic, similar appearances have been reported in scleroderma, and some authors have denied that any specific lesion occurs in systemic lupus erythematosus (Keith, 1940; Stickney and Keith, 1940). On more detailed examination we have been struck by an appearance which is most easily seen in the picro-Mallory preparations. The fuchsinophile material of the thickened loops is flanked on either side by a thin blue-staining line. It is as if the red staining substance had been forced into the basement membrane which has become split (Plate 32, Fig. 7). It has been suggested by Jones (1951) that both epithelial and endothelial basement membranes exist in the glomerular tufts, the two membranes normally being in close contact but with a potential inter-

stitial space between them. The appearance we have noted may possibly result from the deposition of fuchsinophile material between the basement membranes, which are in consequence separated. The nature and pathogenesis of the 'wire-loop' lesion have been discussed by Klemperer, Pollack, and Baehr (1941), Teilum (1948), and Klemperer (1952). The lesion is often associated with hyaline 'thrombi' in the lumina of the capillaries. The thrombi consist of a homogeneous eosinophile substance which gives the same staining reactions as the material in the loops. In long-standing cases the thickened glomerular walls appear to fuse with the thrombi to form large hyaline masses, as in our patient J, who died from renal failure (Plate 32, Fig. 8). Other changes in the glomeruli include increased cellularity of the tufts, focal necrosis of the tufts, haemorrhages into the capsular spaces, adhesions between tufts and capsules, the occasional formation of epithelial crescents, and glomerular and periglomerular fibrosis. These lesions are less characteristic than the 'wire-loops'; in our series they were well-marked only in Case E, in which there were also prominent lesions of the small renal arteries and arterioles, and they are possibly secondary to the vascular changes. The renal tubules may be slightly dilated, and their lumina often contain albuminous casts; occasionally a few red cells and polymorphs are present. The epithelial cells may show cloudy swelling, fatty infiltration, and hyaline droplet degeneration. In the renal stroma we have observed lymphocytic infiltration (Case E), localized deposits of hyaline material around glomeruli and tubules (Case B), and interstitial fibrosis (Case J).

Skeletal muscles. Focal collections of lymphocytes in the voluntary muscles have been reported by several workers (Klemperer, Pollack, and Baehr, 1941; Gibson, Kersley, and Desmarais, 1946; Clawson, Noble, and Lufkin, 1947). Traut and Campione (1952) have described degeneration of muscle-fibres, scarring, and cellular infiltration. One of our fatal cases showed fibrinoid degeneration of the connective-tissue stroma with marked inflammatory cell infiltration (Plate 33, Fig. 9).

Nervous system. In spite of the clinical prominence of neurological features, histological changes are often inconspicuous (Tumulty and Harvey, 1949; Russell, Haserick, and Zucker, 1951). Non-specific changes in our series included micro-abscesses (Case H), hyaline thrombi in the small vessels (Case E), and tuberculous meningitis (Case I). Peripheral neuritis resulting from lesions of the vasa nervorum has been reported by Heptinstall and Sowry (1952).

Joints. There appear to be no detailed reports on the histology of the joints in systemic lupus erythematosus, although arthralgia and 'arthritis' are often observed clinically (Slocumb, 1940; Tumulty and Harvey, 1949). We have observed fibrinoid change in the synovial membranes of patient K (Plate 33, Fig. 10).

Discussion

Since its first recognition observers have been aware of a peculiar relationship between discoid lupus erythematosus and the systemic illness. Our observations convince us that these conditions are intimately related, since the discoid

form sometimes develops into the other. The systemic disease, however, more often arises *de novo*. In its acute form recognition is easy, but when subacute or chronic it may be more difficult. We believe that the discoid disease is a morphological skin reaction, denoting sensitivity to an infective focus (often streptococcal or tuberculous), comparable to erythema nodosum and erythema induratum. The type of skin reaction that develops depends on various factors, of which, for lupus erythematosus, the effect of weather on the skin is paramount, while for erythema induratum posture, stasis, and a poor peripheral circulation are required. The more carefully patients with the discoid disease are investigated, the more often does systemic involvement appear probable from raised erythrocyte sedimentation rates, anaemia, leucopenia, hyperglobulinaemia, or other evidence, and it seems to us that no pathological criterion for their differentiation is available, and that the conditions are separate only in a clinical sense. Consideration of the morbid anatomy alone does not justify any conclusion as to the aetiology or nature of the disease, for, as several workers have insisted, similar changes in the connective tissues may be produced experimentally in several different ways (Klemperer, 1947; Baehr and Pollack, 1947; Altshuler and Angevine, 1949). Nevertheless, fibrinoid degeneration is known to occur both in experimentally induced hypersensitive states and in known hypersensitivity reactions in man, such as serum sickness (Duff, 1948). Furthermore, we have in systemic lupus erythematosus evidence of a gross disturbance of the antibody mechanisms, indicated by the presence of increased circulating γ -globulin and the occurrence of multiple antibodies, often auto-antibodies. It is possible that there is a group of diseases associated with disorders of antibody production and antigen/antibody reactions, apart from hypersensitivity in the usual sense of the word. Thus amyloidosis, both in man and in animals, usually follows prolonged stimulation of the antibody defence mechanism, although hypersensitivity of the Arthus type is lacking. An analogy has been drawn by Teilum (1948) between amyloid and the hyaline material in the renal glomeruli, and the periarterial rings in the spleen, of systemic lupus erythematosus. In our experience, however, the material in the glomerular tufts gives the staining reactions of fibrinoid, whereas the periarterial rings always stain like collagen.

It is felt that the ability to produce so many iso-agglutinins supports the concept of antigen/antibody reaction as the basis of this disease process. Wiener (1950) suggested that this condition, as well as thrombocytopenic purpura, occurs in patients with a propensity to develop auto-antibodies, and that this autosensitization of red blood-cells leads to cold agglutination. Our patient Y was seen initially as a case of acquired haemolytic anaemia. It is probable that, like the positive Coombs test which sometimes develops, the L.E. cell phenomenon may be a further example of auto-antibody formation. This concept has been elaborated by Ehrlich (1952), who described the collagen diseases as 'dys-gammaglobulinaemias'.

A constant feature in every reported series of this disease is its sex distribution. In the present series only two patients were male, and this is in accord

with other observations; female patients account for almost 90 per cent. of all series. It should be noted, however, that there is little sex difference with regard to the chronic discoid disease, and as a correlation it may be mentioned that erythema induratum is also virtually confined to women. Furthermore, the majority of cases of systemic lupus erythematosus occur between the ages of 20 and 40 years. Could it be that during this period, when the female endocrine balance is undergoing a regular cycle of fluctuation, the unstable endocrine background may make women more susceptible to disorders of the immune mechanism? It might reasonably be suggested that the pituitary-adrenal apparatus, because it is never working at a stabilized level, may more readily be upset. Mention of the response of these patients to therapeutic administration of cortisone and ACTH has purposely been avoided, for its inclusion would inevitably increase the length of the discussion. As yet the exact means whereby these substances mediate their effect is uncertain, but it is known that inflammatory reactions, whether caused by infection, by trauma, or by antigen/antibody disturbances, are minimized. It is also possible that production of antibody is depressed during their administration. Clinical response is usually striking, particularly if the case be a florid one, but, though our experience with these substances is admittedly small, our impression is that as a therapeutic weapon they have little to offer. In fact the patients' progress following their use is precisely what one would expect if the basic abnormality is a disturbance of the immune mechanism such as we envisage. The fluctuating course of the disease, the recrudescences that may be produced by sunlight or drug sensitivity, and the remissions induced by cortisone, are consistent with this conception.

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Summary

Twenty-six cases of systemic lupus erythematosus have been observed during the past four years. Fourteen were classified as acute, and twelve as subacute, but importance is not attached to such a separation, which may at times be impossible. Only two (8 per cent.) of our patients were male, and the average age was 30 years. Eleven of the whole group are dead at the time of writing, and the pathological findings in seven cases are presented.

The literature is briefly reviewed, and our clinical and pathological findings are compared with those of other observers. We believe that discoid lupus erythematosus represents a cutaneous reaction denoting hypersensitivity, often to an infective focus, while the systemic disease represents a disturbance of the immune mechanism with the production of abnormal antibodies. These two separate facets of the disease may occur independently or together.

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yearly

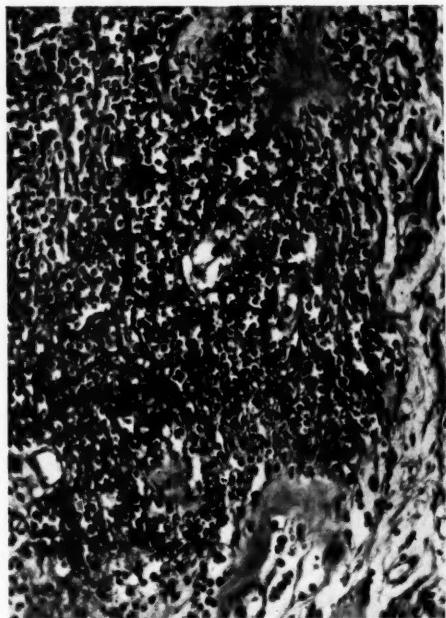


FIG. 1. Case B. Section of visceral pericardium, showing thickened 'fibrinoid' collagen fibres and intense inflammatory cell infiltration (haematoxylin and eosin, $\times 112$)



FIG. 2. Case A. Pulmonary artery with segmental fibrinoid necrosis of wall (appearing black in the Figure) and cellular infiltration (acid-picro-Mallory stain, $\times 112$)



FIG. 3. Case E. Heart opened to show vegetations on mitral valve cusps and papillary muscles

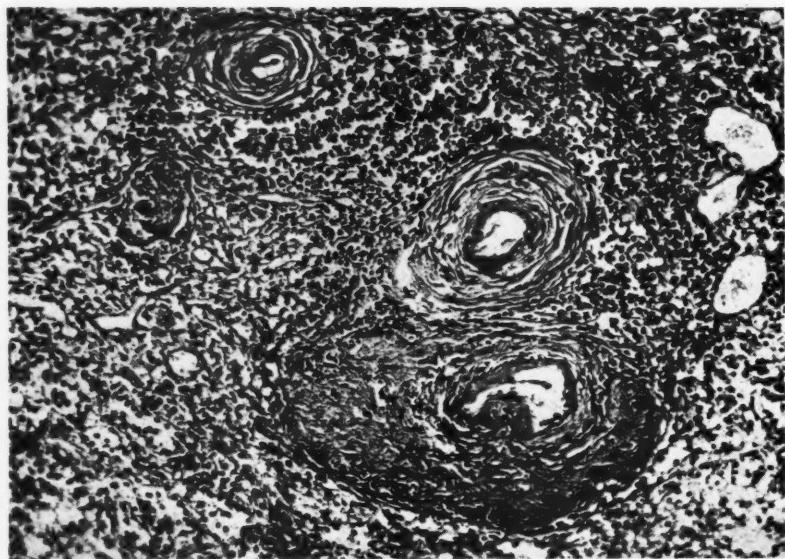


FIG. 4. Case A. Section of spleen, showing concentric laminae of hyaline collagen around small arteries (picro-Mallory stain, $\times 112$)



FIG. 5. Case E. Right kidney ($\times \frac{1}{2}$) showing petechial haemorrhages and infarcts

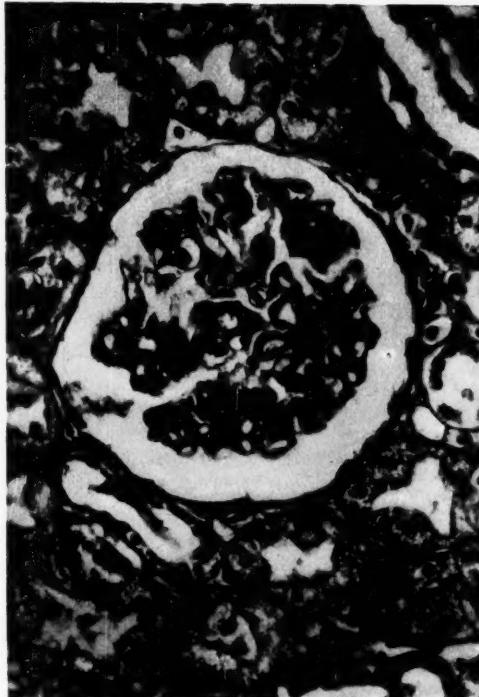


FIG. 6. Case H. Glomerulus with thickened capillary basement membranes ('wire loop' lesions) (picro-Mallory stain, $\times 200$)



FIG. 7. Case H. Higher magnification of thickened loops shown in Fig. 6. The central 'core' of the loop is flanked by fine, darkly stained lines (picro-Mallory stain, $\times 700$)

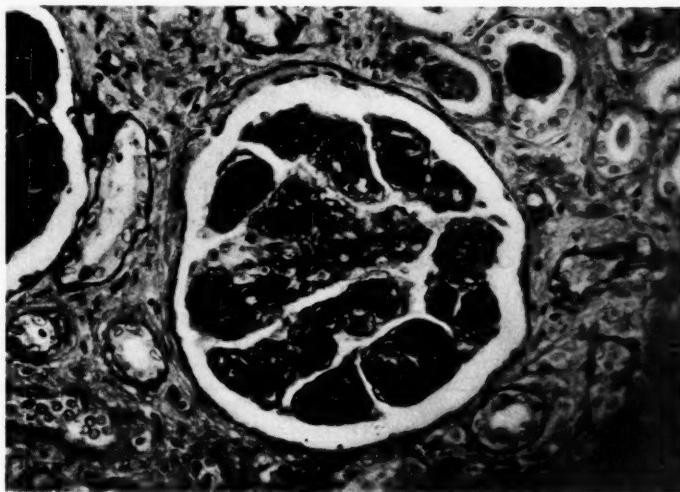


FIG. 8. Case J. Glomerulus with several large, hyaline nodules. Increased lobulation of tuft (periodic-acid-Schiff technique, $\times 200$)

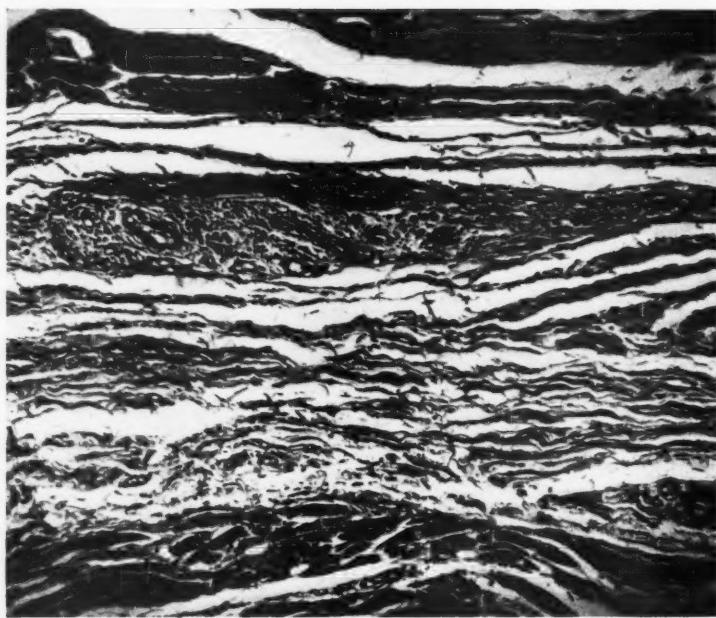


FIG. 9. Case B. Section of psoas muscle showing degeneration of muscle-fibres with oedema and cellular infiltration of connective-tissue septum (haematoxylin and eosin, $\times 80$)



FIG. 10. Case K. Section through metacarpophalangeal joint of right hand, showing fibrinoid degeneration of synovial membrane. The fibrinoid material was stained bright red in the section, and appears black in the photomicrograph (picro-Mallory stain, $\times 50$)

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DISTURBANCES OF AMINOACID METABOLISM FOLLOWING LIVER INJURY¹

A Study by means of Paper Chromatography

By J. M. WALSHE

(From The Medical Unit, University College Hospital Medical School, London)

With Plates 34 to 36

Introduction

LEUCINE and tyrosine crystals were first described as occurring on the cut surface of the liver in cases of acute yellow atrophy by Rokitansky (1849), and crystals of the same two aminoacids were isolated from the urine of patients dying of acute liver necrosis by Frerichs (1860). Since that time much work has been carried out in an attempt to throw further light on the disturbances of amino-acid metabolism which may occur in patients with liver disease. The key role of the liver in deamination was clearly demonstrated by Mann (1927) when he showed that the dog, after total hepatectomy, was unable to form urea from aminoacids; at the same time he found that the functional reserve of the liver was such that, even in a dog with an Eck fistula, removal of 60 per cent. of the liver produced no significant rise in the level of the blood or urinary aminoacids, although it did result in a reduced tolerance to intravenously injected glycine or alanine. More than 85 per cent. of the liver had to be removed before disturbances of aminoacid metabolism became apparent. During the last decade new analytical methods have greatly increased the amount of research on amino-acid metabolism, particularly the introduction of the ninhydrin-CO₂ method for estimating plasma α -aminonitrogen (Hamilton and Van Slyke, 1943), the technique of microbiological assay, and the use of partition paper chromatography (Consden, Gordon, and Martin, 1944). Using the technique of microbiological assay, Frankl and Dunn (1947) found a considerable variation in the normal fasting excretion of aminoacids, together with a well-defined post-absorptive rise. In normal urine Dunn, Camien, Shankman, and Block (1947) found that glycine and histidine were the principal aminoacids, but they were able to identify isoleucine, leucine, lysine, methionine, phenylalanine, tyrosine, threonine, and valine, and after hydrolysis also aspartic and glutamic acid. In patients with acute and chronic liver disease Frankl, Martin, and Dunn (1947) found considerable variations in the excretion of cystine, tryptophane, and histidine, and if the concentration of one of these aminoacids was raised that of the other two tended to be depressed. In patients with cirrhosis of the liver only minor disturbances of aminoacid excretion were detected by Gabuzda, Eckhardt, and Davidson

¹ Received March 16, 1953.

(1952), the most constant abnormality being an increased loss of methionine and tryptophane and a decreased excretion of isoleucine. An impaired methionine tolerance in patients with acute and chronic liver disease was reported by Kinsell, Harper, Barton, Hutchin, and Hess (1948), but Wheeler and György (1948) did not confirm this finding. In a study of the 15 common aminoacids in urine Dunn, Akawaie, Yeh, and Martin (1950) found that a raised excretion occurred in about 20 per cent. of patients with acute and chronic liver disease.

The simple and highly specific method of partition paper chromatography, by means of which it is possible to study simultaneously the behaviour of many aminoacids occurring in body fluids, was first applied to clinical problems by Dent (1946). He was able to demonstrate an abnormal excretion of aminoacids in three out of 12 cases of terminal liver cirrhosis and in one case of acute yellow atrophy, but could find no abnormality in non-fatal hepatitis and the less severe forms of liver injury. In normal urine Dent (1951 b) found that the aminoacids were excreted in definite patterns, characteristic of the individual, and surprisingly independent of exogenous factors. The three common patterns found were (1) glycine alone, (2) glycine and taurine, and (3) glycine and β -aminoisobutyric acid. Glycine, taurine, histidine, and methylhistidine were reported by Stein (1952) as the main aminoacids in six samples of normal urine. A preliminary report of the present study was given by Dent and Walshe (1951), in which they referred to the gross aminoaciduria of acute yellow atrophy, and also to minor changes, involving only a few aminoacids, that may occur in patients with acute hepatitis and cirrhosis of the liver. Thirty-six of the 55 cases reported in the earlier communications are included in the present series. Briefly it can be said that the enormous reserve of the liver applies as much to aminoacid metabolism as to other functions. A study, therefore, confined to total amino-nitrogen concentrations will not reveal any abnormality until the liver is very severely damaged. On the other hand it might be expected that a detailed study of the behaviour of many aminoacids would reveal, relatively early, a disturbance of liver function which involved only a few special aminoacids. Such a study can be carried out by means of paper chromatography, by which it is possible to follow, throughout the course of an illness, changes in the pattern and concentration of any one of many aminoacids occurring in body fluids. It must be added that certain of the commonly occurring aminoacids in urine can only be assayed with difficulty, if at all, by microbiological methods. The object of the present work, therefore, has been to carry out a detailed analysis, by means of paper chromatography, of the changes that may occur in the pattern and concentration of aminoacids in the urine, plasma, and spinal fluid of patients with acute and chronic diseases of the liver.

Methods

The method of study employed has been that of paper partition chromatography as described by Dent (1951a). Specimens of urine and plasma have been analysed from patients suffering from acute and chronic liver disease, obstructive jaundice, and primary and secondary malignant disease of the liver. A

number of cases of hepatomegaly of uncertain origin have also been examined, but are not included here, as their exact classification remains uncertain. Aminoacid-tolerance tests using cystine, cysteine, and methionine will be reported in a later communication. Urine examinations have been made with a constant volume throughout, the volume selected being 50 μ l.; the first morning specimen was chosen so as to avoid, as far as possible, variations in concentration and post-absorptive changes. For plasma analyses constant volumes of ultrafiltered and desalting fluid were taken; the volumes chosen were 125 and 625 μ l. In a small number of cases of hepatic coma it was also possible to examine the spinal fluid; the same technique was employed as for plasma. Every specimen has been analysed oxidized (to demonstrate cystine and methionine, if present) and unoxidized; in a few cases analyses have also been made after hydrolysis with strong hydrochloric acid to break down aminoacid complexes. The results include an interpretation of all analyses carried out in the cases which are reported. When using the method of paper chromatography it is not possible to express the concentration of aminoacids identified in mg. per 100 ml.; but in assessing the results so that they would be approximately quantitative the intensity and, as far as possible, the size of the ninhydrin colour reaction on the paper have been graded numerically against an arbitrary standard, judged under constant lighting conditions, in strengths from 1 to 10; the results are reported in the accompanying Tables in terms of these ninhydrin colour units. In the case of cystine, which it has been possible to estimate quantitatively by means of polarography (Brdicka, 1933), it has been found that the normal daily excretion is of the order of 30 to 60 mg., usually appearing in the urine at a concentration of 20 to 60 μ g. per ml. and corresponding to a chromatographic colour intensity of < 1 to 2 units. For cystine, as for most other amino-acids, each colour unit probably corresponds to a concentration of between 1 and 3 μ g. in the volume of fluid analysed, but accuracy dwindles as the size of the spot on the paper increases.

Results

Classification of results for presentation has given rise to some difficulty, and it has seemed easier to tabulate the findings in clinical rather than biochemical groups. A number of patients could be placed equally well in more than one category; one patient, for instance, had haemochromatosis, developed cirrhosis and primary carcinoma of the liver, and finally died of hepatic failure. As far as possible no patient has been placed in more than one category, but where this could not be avoided it has been made clear in the text. The following classification has been used:

1. Coma of acute hepatic necrosis.
2. Coma of hepatic cirrhosis.
3. Acute hepatitis with positive flocculation tests.
4. Acute or subacute hepatitis with negative or weakly positive flocculation tests.
5. Progressive cirrhosis of the liver with hepatocellular damage.
6. 'Quiescent' cirrhosis of the liver.

7. Obstructive jaundice.
8. Primary carcinoma of the liver.
9. Secondary carcinoma of the liver.
10. Infiltration of the liver.

The study included 119 patients with liver injury and 18 normal controls. Analyses have been made of 325 specimens of urine, 47 of plasma, and eight of spinal fluid from the patients with hepatic disease, and 18 of urine, six of plasma, and three of spinal fluid from the controls. The results are summarized in Table I (urine), Table II (plasma), and Table III (spinal fluid). The figures for aminoacid concentration, under each of the various groups, have been calculated by adding up the entire number of colour units for each individual aminoacid and then dividing by the number of analyses; the average figure is given to the nearest 0.5 ninhydrin colour unit. This method has the disadvantage that case-to-case variations of aminoacid concentration are not demonstrated, nor are the day-to-day changes of pattern that can occur in one patient during the course of the illness. In an attempt to illustrate these two points, details of the urinary aminoacid patterns of eight patients and three normal controls are represented diagrammatically (Figs. 1 to 6), and the relevant clinical details given, in the Appendix. One aminoacid referred to in the Tables, penicillamine, has not been previously reported as occurring in urine. It has been found in the present series only in patients receiving parenteral penicillin therapy. The possible significance of this observation will be considered in the discussion.

Aminoacid patterns in normal urine, plasma, and spinal fluid. 1. *Urine.* Before the significance of abnormal aminoacid patterns can be assessed, it is necessary to have a clear conception of the range of variation that may be found when 50 μ l. of normal urine are analysed. As has been mentioned earlier, Dent (1951 b) found three principal normal patterns, the commonest in which glycine predominates, the second in which glycine and taurine predominate, and the third in which the two main aminoacids are glycine and β -aminoisobutyric acid.

These findings have been confirmed, and in Table I the average figures from 18 further controls are reported. A diagrammatic representation of the three variations of normal is included in the Appendix (Fig. 1). Besides the three aminoacids already mentioned, traces of other aminoacids are commonly found, namely cystine, serine, alanine, glutamine, histidine, and methylhistidine. The difference between the concentration of histidine and methylhistidine found in the present series and the much higher concentrations reported by Stein (1952) may well be related to the difference in the protein-content of the diet in Great Britain and the United States. When normal urine is desalted and concentrated and then a volume containing 5,000 μ g. of nitrogen is analysed, instead of 250

Key to Tables. The figures under each group represent the average figures obtained by adding the entire number of ninhydrin colour units, for each aminoacid, and then dividing by the number of analyses. The results are given to the nearest 0.5 unit. Each colour unit represents approximately 1 to 3 μ g. of aminoacid, and is judged by comparing the size and intensity of the ninhydrin reaction given by the aminoacid on the paper chromatogram against a standard colour scale, under constant lighting conditions. For details of selected individual cases see Appendix.

TABLE I

Urine Analyses (50- μ l. Samples)

Pattern of aminoacids in normal urine and in the urine from the pathological groups 1 to 10

Number of patients	Normal urine (18)	1. Acute hepatic failure (13)	2. Hepatic coma (cirrhosis) (10)	3. Acute hepatitis (coma) (In coma) (14)	4. Acute hepatitis (floculation tests positive) (Acute illness) (32)	4. Acute hepatitis (floculation tests negative) (Acute illness) (39)	5. Cirrhosis active* (16)*	5. Cirrhosis active* (17)	6. Cirrhosis inactive* (15)	7. Obstructive jaundice (10)	8. Primary carcinoma of liver (Secondary) (7)	9. Secondary carcinoma of liver (7)	10. Infiltrations of liver (7)
Number of analyses	18	26	18	32	35	2.0	3.5	2.0	2.5	2.0	12	12	9
Aminoacid:													
Cystine	1.0	4.0	5.0
Penicillamine	..	0.5	0.5	1.0
Aspartic acid	..	1.5	0.5	1.0
Glutamic acid	..	3.5	1.5	2.0	0.5	1.5
Phosphoethanolamine	0.5	0.5
Glycine	3.0	8.0	5.0	6.0	3.5	6.0	4.5	3.5	2.5	2.5	0.5
Serine	1.5	4.5	4.5	2.0	2.0	1.0	1.0	1.0	1.0	1.0	4.5	4.5	0.5
Taurine	..	1.0	1.5	1.5
Alanine	0.5	5.0	5.0	3.5	3.5	1.0	1.0	1.0	1.0	1.0	3.0	2.5	1.0
Glutamine	0.5	5.0	2.5	2.0	2.0	0.5	1.5	1.5	2.0	0.5	1.5	1.0	1.0
Threonine	3.0
Histidine	0.5	4.5	1.0	3.0	3.0	0.5	0.5	1.0	1.0	1.0
β -aminoisobutyric acid	0.5	2.0	4.0	3.0	3.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	0.5
Methylhistidine	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	1.0	1.0	0.5	0.5	0.5
Proline	..	0.5
Hydroxyproline
β -alanine
Citrulline
'Under alanine'
Lysine	..	1.0	0.5
Arginine	..	1.0	0.5
2-aminobutyric acid	..	0.5	0.5
2-aminobutyric acid
Valine	..	1.5	0.5	0.5
Leucine/isoleucine	..	1.5	1.0	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Phenylalanine	..	1.5	1.0	0.5
Tryptophane	..	2.5	1.0	1.0
Tyrosine	..	2.5	1.5	0.5
Ethanolamine	..	1.5	1.0	0.5
Methionine	0.5
Methionine sulphoxide
Methionine sulphone
Asparagine	..	0.5
'Fast arginine'	..	0.5
Other unknowns (number)

* Active cirrhosis: in this column the mean figures are derived from the maximum reading in each case

μg . as advocated by Dent (1949) for routine diagnostic purposes, the following additional aminoacids can be identified: tyrosine, tryptophane, phenylalanine, leucine, valine, ethanolamine, arginine, lysine, and threonine, together with a number of unidentified ninhydrin colour reactors.

2. *Plasma*. Normal plasma has a different pattern of aminoacids to that found in normal urine, even when allowance is made for the greater volume analysed

TABLE II
Plasma Analyses (625- μl . Samples)

Pattern of aminoacids in normal plasma and in plasma from those pathological groups in which abnormalities were detected

Number of patients	Normal	Acute hepatic	Hepatic coma	'Active'	'Inactive'
	plasma (8)	failure (13) (In coma)	(10)	cirrhosis (16)	cirrhosis (15)
Number of analyses	6	10	7	13	3
Aminoacid:					
Cystine	2.0	3.5	5.0	4.0	4.0
Penicillamine	0.5
Aspartic acid	0.5	2.0	1.0	1.0	..
Glutamic acid	3.5	7.0	6.0	5.5	3.5
Phosphoethanolamine	..	0.5	..	0.5	..
Glycine	6.0	7.5	7.0	6.0	7.0
Serine	4.0	7.0	5.5	4.5	5.0
Taurine	2.0	3.5	3.0	2.0	3.0
Alanine	7.0	9.0	8.0	7.5	7.5
Glutamine	7.0	9.5	7.5	7.0	7.5
Threonine	2.0	5.0	2.0	2.5	3.0
Histidine	1.0	2.5	1.5	0.5	0.5
β -aminoisobutyric acid	0.5	1.5	2.0	0.5	0.5
Methylhistidine	0.5	0.5	..
Proline	0.5	2.5	1.5	1.0	1.5
Hydroxyproline
β -alanine	..	0.5
'Under alanine'	..	0.5
Citrulline	1.0	1.0	1.5	0.5	1.0
Lysine	3.0	6.0	5.0	3.0	2.5
Arginine	1.0	4.0	2.0	2.0	1.5
α -aminobutyric acid	1.0	0.5
γ -aminobutyric acid	..	2.5	2.0	1.0	0.5
Valine	7.0	8.0	7.5	7.5	5.5
Leucine/isoleucine	7.0	8.0	7.5	6.0	5.0
Phenylalanine	2.0	5.0	4.0	2.5	2.0
Tryptophane	0.5	1.0	1.0	0.5	..
Tyrosine	2.0	5.0	4.5	3.5	3.5
Ethanolamine
Methionine	0.5	5.0	3.5	2.5	2.0
Methionine sulphoxide	..	1.0	0.5
Methionine sulphone	..	0.5
Asparagine
'Fast arginine'
Other unknowns (number)	..	(3)	(1)

(625 μl .). The essential aminoacids are present in a very much higher relative concentration. The following aminoacids have been identified in 625 μl . of normal plasma: tyrosine, phenylalanine, leucine, valine, lysine, alanine, glutamine, threonine, glycine, serine, glutamic acid, and traces of proline, methionine, α -aminobutyric acid, arginine, histidine, taurine, aspartic acid, and cystine.

These aminoacids are substantially those illustrated by Dent and Rose (1951) and by Walshe (1951) as occurring in normal plasma. Table II includes the average figures from six analyses of normal plasma.

3. *Cerebrospinal fluid.* Normal spinal fluid contains glutamine as the principal ninhydrin colour reactor; it is present in a concentration equal to, or greater

TABLE III
Cerebrospinal Fluid Analyses (625- μ l. Samples)

Pattern of aminoacids in normal spinal fluid and in the spinal fluid of patients in hepatic coma

Number of patients	Normal (3)	Acute hepatic failure, in coma (3)		Hepatic cirrhosis, in coma (4)	
		(Died) 2	(Recovered later) 1	(Died) 1	(Recovered later) 3
Number of analyses	3	2	1	1	3
Aminoacid:					
Cystine	1.0	0.5
Glutamic acid	1.0	1.5	2.0	4.0	2.5
Phosphoethanolamine	..	0.5
Glycine	1.0	2.5	1.0	3.0	1.5
Serine	2.0	2.5	3.0	3.0	2.5
Taurine	..	1.5
Alanine	2.0	3.0	..	5.0	3.0
Glutamine	7.0	10.0	10.0	10.0	10.0
Threonine	..	2.5	2.0	..	0.5
Histidine	1.0	2.0	..
β -aminobutyric acid	1.0	1.0
Methylhistidine	1.0	..
Lysine	..	1.0	0.5	1.0	..
Arginine	..	1.0	..	1.0	..
α -aminobutyric acid	..	0.5	1.0	4.0	..
Valine	1.0	2.5	3.0	6.0	1.5
Leucine/isoleucine	2.0	2.0	2.0	7.0	1.5
Phenylalanine	..	3.5	1.0	5.0	1.5
Tryptophane	2.0	..
Tyrosine	..	4.5	1.0	5.0	2.0
Methionine	..	3.5	3.0	2.0	0.5
Methionine sulphoxide	..	1.5	..	1.0	0.5

than, that in which it appears in plasma. Traces only of leucine, valine, alanine, glycine, and serine can be detected. Serine is present in a concentration slightly greater than glycine, thus reversing the normal plasma ratio; methionine has not been detected in 625 μ l. of normal spinal fluid. The mean values found in three normal spinal fluids are given in Table III.

Class 1. *Massive hepatic necrosis with coma* (Plate 35, Fig. 9). This group consists of 13 patients, 10 female and three male. Eight patients showed the classical clinical and biochemical picture of acute yellow atrophy; in two the illness was somewhat less acute and the aminoaciduria less striking, and one of these two patients is also included in the group 'acute hepatitis with negative flocculation tests,' as her illness was of this type for six weeks. Two examples are also included in which there was, in addition, extensive secondary carcinoma of the liver, and it is not clear whether the hepatic necrosis was due to a homologous serum hepatitis or to compression of the vessels in the porta hepatis by neoplastic glands; both patients showed a very heavy aminoaciduria. The

remaining patient, a man with portal hypertension, lapsed into coma after operation for the construction of a portacaval shunt; details are given in the Appendix. Two of the patients with fulminant hepatitis, and the patient who underwent operation, recovered; in the remaining 10 it was possible to confirm the diagnosis histologically at post-mortem examination. Altogether 38 specimens of urine, 11 of plasma, and three of spinal fluid were examined. Included in Table I are the average figures from 26 specimens of urine collected during the acute period of the illness; the other 12, obtained during the convalescent phase from the three patients who recovered, approximated closely to the normal. Similarly the results of 10 of the analyses of plasma and all three analyses of spinal fluid are given in Tables II and III respectively. A diagrammatic representation of the aminoacid pattern in the urine, showing the maximal abnormality observed, in three cases of fulminant hepatitis, is given in the Appendix (Fig. 2), together with detailed results from the patient who underwent operation (Fig. 4).

Reference to Tables I and II makes it clear that, while a large number of aminoacids have been detected in both blood and urine, only about half of these occur commonly in very great excess. With recovery the aminoacid picture may return rapidly to normal; in one case this occurred in 36 hours, and before clinical evidence of recovery was apparent. While individual variation, which cannot be shown in the Tables, is very great, there are certain features common to both plasma and urine which call for comment, as they seem to indicate especially severe liver damage. Perhaps the most striking of these is the reversal of the normal alanine/glutamine concentration ratio, so that glutamine may come greatly to exceed alanine; another striking abnormality is the high concentration of methionine which may be reached in the plasma, and also that of ethanolamine in the urine. That these changes are due to a specific disturbance of aminoacid metabolism, and not simply to the liberation of free aminoacids from autolysing hepatic parenchymal cells, has been suggested by chromatographic analyses of *in vitro* autolysed liver; in such analyses these abnormalities of pattern have never been found. It can also be seen from the Tables that a small number of unidentified ninhydrin reactors have, on occasions, appeared in plasma and urine. In one case of fulminant hepatitis there was found in the plasma, in rather high concentration, what was probably an unidentified sulphur-aminoacid. It is believed that methionine sulphoxide may also be found in the plasma in such cases, and in one case the sulphone was found; the possible significance of this occurrence has been discussed elsewhere (Walshe, 1951).

The changes in the spinal fluid are recorded in Table III. As in the plasma, there was a general rise in aminoacid concentration, but the choroid plexuses did not appear to be equally permeable to all aminoacids. Glutamine may have been actively secreted at the choroid plexus, and achieved a very high concentration; serine seemed to penetrate the barrier more easily than most other amino-acids, as did methionine and its sulphoxide. The resistance of the barrier to methionine apparently decreased in liver failure, as it was not found possible to demonstrate the presence of this aminoacid in the spinal fluid of a patient,

without liver damage, who was given 5.0 gm. of methionine two hours before a diagnostic lumbar puncture; in these circumstances a considerable increase of methionine in the plasma had been induced.

Class 2. Progressive cirrhosis of the liver with hepatic coma (Plate 35, Fig. 10). This group is made up of 10 patients, four male and six female; in seven the episode of coma was fatal, but three regained consciousness; one died one year later. The other two have survived eight and 11 months respectively at the time of writing. The eight patients seen personally all suffered from severe parenchymal liver damage, and two were found at post-mortem examination to have primary malignant disease in the liver, in one case secondary to alcoholic cirrhosis, and in the other to haemochromatosis. Altogether 23 specimens of urine, seven of plasma, and five of spinal fluid were examined. Eighteen of the urine samples were collected during episodes of coma, and these are reported in Table I; the results of all the plasma analyses are given in Table II, and four of those obtained from spinal fluid are to be found in Table III; the reason for omission of one of the spinal fluid analyses will be made clear in a subsequent paragraph. A very wide variation occurred, in this group, in the patterns of aminoacids found in the urine of different patients; the pattern in two cases closely approached the degree of abnormality found in Class 1. The average figures, however, show that the disturbance of aminoacid metabolism was less generalized than in the cases of massive hepatic necrosis, and in most of the patients only three or four aminoacids showed a significant abnormality. The concentration of cystine was almost invariably elevated, and frequently β -aminoisobutyric acid and ethanolamine were also affected. On a small number of occasions taurine was increased, but this did not occur sufficiently often to raise the average figure; less striking, but more constant, was the excess in the urine of tyrosine, phenylalanine, leucine, and valine; a heavy loss of methionine was only met with on one occasion; the plasma findings in this case are shown in Figs. 7 and 8 (Plate 34). The exact importance of methylhistidine is not clear; its occurrence was stressed in an earlier publication (Dent and Walshe, 1951), but is now thought to be dietary in origin rather than of metabolic importance (Datta and Harris, 1951). Twenty-three different aminoacids were identified in the specimens of urine from patients in this group. The changes met with in one case during the episode of coma and after recovery are illustrated in the Appendix (Fig. 5). Study of the plasma has yielded less information than examination of the urine, probably because a small rise in the plasma concentration of an individual aminoacid may not certainly be detectable on the chromatogram, and yet may exceed the renal threshold for that aminoacid and lead to a big increase of excretion in the urine. Plasma studies, however, confirmed the increase of cystine, and also showed a rather high concentration of the aromatic aminoacids and of methionine and glutamic acid. In one case the methionine concentration exceeded that of any other aminoacid (Plate 34, Figs. 7, 8), a finding which was clearly related to the methionine supplements given to the patient. Of the four patients whose spinal fluid was analysed, three recovered, and in these the abnormality in the fluid was

significantly less than in the patient who died. In the latter patient the concentration of glutamine was very greatly increased, and that of many other amino-acids was also significantly elevated; methionine and its sulphoxide were both apparently present. In one of the other three cases it was possible to examine the spinal fluid before and during an intravenous infusion of glutamic acid. The second sample (not included in Table III) was obtained 10 minutes after commencement of the infusion, when approximately 10 gm. of the aminoacid had been administered. There appeared to be an increase in the concentration of both glutamic acid and glutamine in the second sample. The patient recovered consciousness about six hours after the infusion had been completed. The conclusion to be drawn from this group of cases is that the combination of cystine, β -aminoisobutyric acid, and ethanolamine in the urine in excess, with or without excess of other aminoacids, is indicative of severe liver damage.

Class 3. Acute hepatitis with positive serum flocculation tests (Plate 35, Fig. 11). This group consisted of 14 patients, six male and eight female. Twelve cases were classical examples of acute virus hepatitis with a short, sharp prodromal illness, and a period of icterus lasting two to three weeks. The remaining two cases were examples of toxic hepatitis; one was due to prolonged chloroform anaesthesia during childbirth, and the other probably to a bout of acute alcoholism associated with an episode of acute pancreatitis. Of the 51 urine specimens examined, 32 were obtained in the acute phase of the illness, and are reported in Table I; the 19 specimens collected after recovery showed a rapid return to the normal pattern. The patient subjected to chloroform anaesthesia showed the greatest abnormality in this group, although she showed little clinical evidence of liver injury; biochemical recovery was complete in 48 hours. In the patients who had acute virus hepatitis, the pattern of urinary aminoacids early in the illness could well be called that of 'acute yellow atrophy in miniature', (Appendix, Fig. 6 b) using the words with which Eppinger described the histological changes in this condition. There was an excessive excretion of many aminoacids, as in acute yellow atrophy, although the total concentrations were much lower. The aminoacids which increased in concentration first were leucine, valine, phenylalanine, and tyrosine, and there was at the same time a small rise in the concentration of those normally present. Rather characteristic was the way in which the pattern of aminoacids in a given case varied from day to day, suggesting that different enzyme systems were affected at different stages of the disease. The average figures of the results in this group (Table I) show that, apart from the appearance of tyrosine, phenylalanine, leucine, and valine already mentioned, there was a significant increase in the excretion of cystine, glutamic acid, taurine, β -aminoisobutyric acid, and methylhistidine; ethanolamine was occasionally found. Twenty-one different aminoacids were identified in the urine from patients with acute hepatitis; only one of these was unknown, namely 'fast arginine' (Dent, 1948).

Class 4. Acute hepatitis with negative or weakly positive flocculation tests (Plate 36, Fig. 12). In this group were 17 patients, 10 male and seven female. The illness appeared to be a virus hepatitis in which the onset was insidious and

the course prolonged; in one case the duration from onset to a fatal termination was 11 months, and throughout this time, in spite of intense jaundice, the protein flocculation tests were negative. The diagnosis was substantiated by biopsy and post-mortem examination. A second patient in this group died; after a month's illness, thought to be obstructive jaundice, her condition suddenly deteriorated, and she died in cholaemia. This terminal episode is included in Class 1. All the remaining patients recovered spontaneously, but two were subjected to exploratory laparotomy, because a diagnosis of obstruction to the main duct was suggested on both clinical and biochemical grounds. Thirty-nine specimens of urine and one of plasma were analysed for aminoacids. The results of the urine examinations are reported in Table I; the single plasma examination revealed no abnormality. In the large majority of patients there appeared to be no significant disturbance in the urinary excretion of aminoacids (Appendix, Fig. 6a). As this type of case often presents a most difficult problem in diagnosis from obstructive jaundice, this finding was disappointing. In one case ethanolamine was repeatedly found in the urine as an isolated abnormality; the only other patient to show an abnormal excretion of aminoacids was the patient dying in cholaemia, referred to above. The illness of one patient, a diabetic, was complicated by the perforation of a duodenal ulcer; for three days after an operation for repair of the perforation he had a well-marked increase of aminoacids in his urine. This finding was in keeping with the definite 'post-operative response' reported previously by Dent and Walshe (1951). In all these cases the diagnosis was confirmed either by the eventual outcome of the illness, by biopsy, at laparotomy, or at post-mortem examination.

Class 5. Progressive cirrhosis of the liver with hepatocellular damage (Plate 36, Fig. 13). The 16 patients included under this heading comprise six men and 10 women. During the period of study four patients died, and contact was lost with five, of whom two are believed to have died. Five patients gave a clear history of a preceding hepatitis, and these had, clinically, the most severe illness; two have died, and the prognosis of the survivors appeared to be extremely poor. There were three chronic alcoholic patients, and one of these also gave a history of a recent attack of homologous serum hepatitis. In only three other cases could aetiological factors be suspected, namely ulcerative colitis, syphilis, and gall-stones with chronic cholecystitis. There remain six patients in whom no underlying factor could be incriminated; four of these had the hypercholesterolaemic type of chronic hepatitis. Of the four patients who died, the terminal episode was pneumococcal peritonitis in one, haemorrhage from oesophageal varices in one, and parenchymal liver failure in two (one of whom is also included in Class 2). During the course of the investigation opportunity was taken to examine 56 specimens of urine and 13 of plasma; in some cases the follow-up period has exceeded two years. The results of the urine analyses are summarized in Table I; only the most abnormal specimen from each patient is included. Such a Table fails to show the variation of pattern in aminoacid excretion that occurs in different patients, or in a single patient at different stages of the illness. In the Appendix (Fig. 3) is a diagrammatic

representation of the changes that occurred in the excretion of aminoacids in one patient in the course of a year. With these reservations in mind, certain conclusions can be drawn from the figures in the Table; cystine, taurine, β -aminoisobutyric acid, and ethanolamine were the aminoacids most frequently excreted in excess, but the concentration of all the commonly occurring aminoacids was greater than normal, and tyrosine, phenylalanine, leucine, and valine could frequently be detected. Plasma studies revealed no very great abnormalities, but cystine, glutamic acid, and methionine were increased in concentration more often than other aminoacids.

Opportunity was taken to investigate the effect of two therapeutic substances on the excretion of aminoacids in certain patients. The substances studied were choline and corticotrophic hormone (ACTH). The use of choline was suggested by the presence of ethanolamine ($\text{CH}_2(\text{NH}_2)\text{CH}_2\text{OH}$) in the urine, as the latter implies a possible deficiency of methyl groups in the metabolic pool. There was no clear-cut evidence that choline reduced the excretion of ethanolamine, although in three of the four patients so treated there appeared to be a coincident generalized reduction in the urinary aminoacids. In two of these cases the plasma choline level was estimated by biological assay (Bligh, 1952), and was within normal limits; this fact suggests a mechanism of ethanolamine loss other than a methyl-group deficiency, and the possibility of a partial block in the process of transmethylation must be considered. Fig. 3b in the Appendix illustrates the reduction in aminoaciduria which occurred simultaneously with the administration of choline to a patient in this group. ACTH also appeared to have no direct influence on the pattern of aminoacids found in the urine of the three patients studied, in spite of the claim (György, 1951) that it leads to an increased excretion of cystine.

In the remaining groups (Classes 6 to 10) no major abnormalities were detected. The average results of the urine examinations in each group are given in Table I, and of the plasma analyses in Class 6 only ('inactive' cirrhosis) in Table II.

Class 6. 'Inactive' cirrhosis of the liver (Plate 36, Fig. 14). Fifteen patients, six male and nine female, are included in this class. The basis of separation from the preceding group ('active' cirrhosis) is that these patients showed less constitutional disturbance, and the plasma-proteins and serum flocculation tests showed less deviation from the normal. Four patients had no symptoms directly attributable to their liver condition; one suffered from biliary cirrhosis, and died eventually as a result of prolonged obstructive jaundice due to carcinoma of the pancreas, while the disability in the remaining 10 patients could be directly attributed to portal hypertension, manifesting itself as ascites in three, haemorrhage in six, and both ascites and haemorrhage in one. Of the patients with uncomplicated haemorrhage two died, one three years and one 10 years after the initial bleeding; of the three survivors, one had had her first haematemesis 14 years, one four years, and one one year previously; the latter patient certainly had well-established varices 15 months before her first haemorrhage. One of the three patients with ascites has been followed up for

five years after a hepatic vein thrombosis; the other two have been lost sight of, one after one year and one after two years. The remaining patient certainly survived the onset of ascites by 14 years and the first haemorrhage by 10 years. Table I gives the results of 33 urine analyses, and these show no significant variation from the normal. The three plasma results reported in Table II show nothing more than a tendency for cystine and methionine to be increased. Two results are not included because they both closely followed a haematemesis, and were thought not to give a true picture of the patient's aminoacid pattern.

Class 7. Obstructive jaundice. This group consisted of 10 patients, five male and five female; in only one was the picture complicated by cholangitis. In five cases the obstruction was due to malignant disease, and in four to stones or stricture of the common bile-duct; in one case no cause was found at operation. Sixteen specimens of urine were examined, and four of plasma; the latter did not deviate significantly from normal, and are therefore not included in Table II. The urine results given in Table I show average figures very similar to those in the control group. On two occasions the aminoacid concentration appeared to be well below normal, but minor disturbances of pattern were met with, the concentration of cystine and taurine being occasionally increased. Only once was the picture of aminoacids in the urine sufficiently abnormal to suggest a diagnosis of hepatitis.

Class 8. Primary carcinoma of the liver. Ten examples of this relatively rare condition became available for study, but only seven are included in this group. Two are reported in Class 2, because when first seen they presented the picture of cirrhosis in hepatic coma. The third patient not included showed a very remarkable abnormality in that she excreted between 0.5 and 1.0 gm. of ethanalamine daily (Dent, Fowler, and Walshe, 1951); she was the subject of a detailed metabolic study published elsewhere (Dent and Walshe, 1953). In all the remaining seven cases the diagnosis was confirmed histologically. Only 12 analyses of urine and two of plasma, out of a total of 48 urine and nine plasma examinations carried out, are therefore available for inclusion in this group. No specific abnormalities were found in the plasma, and the urine results only are reported (Table I).

Class 9. Secondary carcinoma of the liver. Only patients with moderately severe secondary carcinomatous involvement of the liver were studied; three of these had obstructive jaundice in addition. No important abnormalities were found in any of the 12 samples of urine and one of plasma that were examined.

Class 10. Infiltrations of the liver. Seven patients were studied; three had haemochromatosis, two had generalized sarcoidosis and hepatomegaly, one had Gaucher's disease, and one had alveolar hydatid involving the liver. No important abnormalities were found in any of the nine specimens of urine examined.

Discussion

The results described in the preceding section show clearly that disturbances in the urinary excretion of aminoacids occur both in acute and in severe chronic liver disease. The relatively small number of plasma studies have confirmed

the view that these abnormalities are due, not to changes in the renal threshold, but to a raised concentration in the plasma of the aminoacid concerned. As a general rule a disturbance of the pattern of aminoacids in the urine is more common than an increased concentration, and the degree of abnormality is roughly parallel with the severity of the underlying liver damage. As the clinical picture in acute liver injury can vary from a mild to a rapidly fatal illness, so the disturbance of aminoacid excretion in the urine can vary from a small increase of one or two aminoacids to a gross aminoaciduria which commonly, though not invariably, heralds a fatal outcome. In patients with the most severe illness the disorder of aminoacid metabolism is so generalized that it is difficult to single out any one aminoacid for particular mention except methionine, which appears to be increased in concentration out of proportion to the others. In chronic liver disease it is more common for one or more aminoacids to be excreted in excess, although in the terminal coma of cirrhosis a generalized aminoaciduria may be found. As in the acute cases, there appears to be a correlation between the severity of the illness and the degree of disturbance of aminoacid metabolism. Here again, however, a reversal of the aminoacid disturbance can be associated with a clinical improvement in the condition of the patient (Appendix, Fig. 3). The aminoacids most frequently excreted in excess are cystine, taurine, and β -aminoisobutyric acid, sometimes associated with tyrosine, phenylalanine, and ethanalamine. In the plasma often the most significant abnormality was a marked rise in the concentration of methionine. In mild liver injury, focal lesions of the liver, and obstructive jaundice significant disturbances of aminoacid metabolism have not been encountered.

While changes in aminoacid metabolism are commonly confined to two or three aminoacids, such abnormalities as may occur, even if well-marked, are often fleeting and are easily missed if repeated urine examinations are not made. This is especially the case in hepatic cirrhosis, in which an increased excretion of aminoacids follows the activity of the disease process, although fluctuations in the concentration of individual aminoacids have also been observed during the course of an attack of virus hepatitis (Dent and Walshe, 1951). While it is clear that the finding of a heavy aminoaciduria is of immediate value in gauging the severity of acute hepatitis or of hepatic cirrhosis in an individual patient, it is not yet certain whether cases of acute hepatitis are more likely to proceed to post-necrotic scarring if they have shown a marked disturbance of aminoacid metabolism; only a long-term follow-up study can answer this question.

A further point of interest that has emerged from the present studies is the rather sharp division of the cases of acute hepatitis into two groups. The classical picture of the illness, occurring in a young adult, and showing a short febrile pre-icteric phase with marked constitutional disturbance, followed by a period of mild or moderate jaundice resolving completely in three or four weeks, and characterized by strongly positive flocculation tests, was commonly associated with a mild or moderate generalized aminoaciduria which cleared completely with recovery of the patient. The second type of case, found more

commonly among the later age-groups, was more insidious in onset and more prolonged, and was associated with deep jaundice and negative or very weakly positive serum flocculation tests; these patients showed little or no disturbance of aminoacid metabolism. As a possible explanation the suggestion is put forward that the difference between the two groups could best be explained in terms of the anatomical situation of the lesion in the liver lobule. The biopsy specimens obtained from three patients in the second, more insidious type of disease support the theory that the lesion may be situated chiefly in the portal tracts (Plate 36, Fig. 12) rather than in the classical centrilobular situation (Plate 35, Fig. 11) described by Dible, McMichael, and Sherlock (1943). Similar periportal lesions have been described by Watson and Hoffbauer (1946) in their account of chronic or cholangiolitic hepatitis. Such a periportal lesion would allow the products of cell death to pass down the sinusoids, past functioning parenchymal cells, before escaping into the general circulation. It is also possible that the high-protein diets now used in the therapy of liver disease may contribute, at least in part, to the aminoaciduria of acute hepatitis. Datta and Harris (1951) have shown that the output of methylhistidine is almost certainly related, in normal persons, to the amount of animal protein in the diet, being derived from anserine, a normal constituent of vertebrate muscle.

The sulphur-aminoacids cystine and methionine have both been used in the therapy of liver disease, as has choline, and more recently corticotrophic hormone (ACTH). It has been possible in the present series to make certain observations on the part played by these agents in the general aminoacid economy. ACTH was used on three occasions in patients who had cirrhosis; it did not appear to influence the pattern of aminoacids in the urine in any way, but in all three cases the initial disturbance of aminoacid metabolism was only mild. On the other hand choline administration was followed, in three out of four cases, by a generalized reduction in aminoaciduria, although it did not reduce the excretion of ethanolamine. This biochemical improvement coincident with choline therapy cannot be evaluated in such a small series, and may have been simply a manifestation of the improvement that is known to follow rest in bed and adequate diet in patients with chronic liver injury (Klatskin and Yesner, 1949). This is perhaps a convenient point at which to consider the place of methionine and cystine supplements in the treatment of liver disease. While there is no doubt that these two aminoacids are essential in the liver economy (Himsworth and Glynn, 1944; Glynn and Himsworth, 1944), there is no very satisfactory evidence that either modifies the course of acute hepatitis in man (Peters, Thompson, King, Williams, and Nicol, 1945; Cayer, 1947; Ström, 1950), and one patient described by Watson (1949) lapsed into coma on each occasion that methionine was given. Dent (1947) doubted the value of methionine or cystine supplements in patients who could be shown by chromatography to have an adequate body saturation of these aminoacids. The present investigation has shown that the concentration of methionine and cystine in the blood in severe hepatitis may sometimes reach very high levels, and may therefore possibly achieve a toxic concentration. An excess of cystine in the

diet has been shown to produce haemorrhagic liver necrosis in rats (Earle and Victor, 1942), and both sulphur-aminoacids produce acidosis by virtue of their being chiefly metabolized to inorganic sulphates. In view of the recent work of Ackermann (1951), who showed that methionine was necessary to certain influenza Type-A viruses for the host/virus interaction system and virus propagation, it is at least theoretically possible that a similar relationship exists for the hepatitis virus in man. It may be that a very high concentration of methionine in the plasma is more favourable to virus growth than to liver-cell repair.

Mention has been made earlier of the finding of penicillamine ($\beta\beta'$ -dimethylcysteine) in the urine of patients receiving parenteral penicillin therapy. Evidence for the identification of this aminoacid in urine has not yet been published, but an incompletely purified preparation has been shown to contain the expected elements carbon, hydrogen, nitrogen, sulphur, and, by difference, oxygen. On chromatographic analysis, using three different pairs of solvents, it behaves in a fashion identical with a sample of synthetic penicillamine both before and after oxidation. Finally penicillamic acid, a derivative of penicillamine, has been prepared from urine in crystalline form, and has been shown by elementary analysis to have a composition identical with synthetic penicillamic acid. There can be little doubt that the penicillamine found in urine is derived from penicillin that has been administered therapeutically. Penicillamine was found in the urine of patients with liver injury who were receiving a penicillin dosage that did not lead to penicillaminuria in normal subjects; but when a sufficiently large dose of penicillin (of the order of two million units) was given to a normal subject, penicillamine could be detected in the urine. In the Appendix (Fig. 5) is an example of the urine of a patient in hepatic coma who was excreting a large concentration of penicillamine, although the penicillin dosage was only 300,000 units twice daily. The excessive excretion of penicillamine in patients with liver injury could be due either to increased formation in the body or to decreased utilization, but at present the exact significance of this finding is not clear. Wilson and Du Vigneaud (1950) have reported that *l*-penicillamine is toxic to growing rats; but the naturally occurring isomer is dextro-rotatory, so that penicillin therapy is probably not contra-indicated in patients with liver injury.

In conclusion I wish to thank Professor M. L. Rosenheim and Dr. C. E. Dent for their advice and encouragement during the course of this work, the physicians on the staff of University College Hospital who permitted me to investigate their patients, and Professor C. Bruce Perry, Dr. R. G. Calvert, Dr. N. F. Coghill, and Professor R. Milnes Walker, who provided me with plasma and urine from patients in hepatic coma. I also wish to thank Dr. Karl Folkers of Merck and Co., Inc., New Jersey, for the samples of synthetic penicillamine, and Mr. A. Bligh for the photomicrographs.

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APPENDIX

Figs. 1 to 6 represent diagrammatically the concentrations of the various aminoacids found in the urine from normal controls and from patients with acute and chronic liver injury. The size of each circle represents the concentration of the aminoacid on the paper chromatogram, as judged by the size and intensity of the ninhydrin colour reaction against an arbitrary scale seen under standard lighting conditions. Fig. 1 shows the aminoacids found in 50 µl. of normal urine, oxidized, and the relative concentrations in the three principal patterns: (a) glycine, (b) glycine and taurine, (c) glycine and β -aminoisobutyric acid. The glycine pattern comprises about 90 per cent. of all normal specimens. Fig. 2. *Massive hepatic necrosis.* This figure represents the most abnormal pattern of aminoacids found in 50 µl. of oxidized urine from three different cases of acute parenchymal liver failure. (a) A woman aged 22 years, who died in coma four days after the onset of jaundice and vomiting. The plasma α -amino-nitrogen was 20 mg. per 100 ml. The histology of the liver is illustrated in Plate 35, Fig. 9. (b) A woman aged 25 years, who died after five weeks' illness with vomiting and jaundice, and was in coma for one week before death. The plasma α -amino-nitrogen was 11.5 mg. per 100 ml. (c) A woman aged 54 years. Five weeks after an abdomino-perineal resection of the rectum she passed rapidly into hepatic coma, and died two days later. This illness was possibly a case of homologous serum hepatitis. Post-mortem examination revealed almost complete necrosis of the liver parenchymal cells. Fig. 3. *'Active' hepatic fibrosis.* This figure shows the pattern of aminoacids in 50 µl. of oxidized urine of a woman of 62 years with cirrhosis of the liver, icterus, and positive serum flocculation tests. Plate 36, Fig. 13 shows the liver histology at the time of the first chromatogram (a) (27.4.50). At the time of the second chromatogram (b) her condition had improved after two months of rest in bed, adequate diet, and choline supplements (2 gm. daily). Shortly after this she was able to return home. The third examination (c) (23.3.51) was made after her second admission to hospital. The patient died of liver failure three months later. Fig. 4. *Hepatic coma.* This figure shows the results of three urine aminoacid analyses from a patient passing into, and recovering from, hepatic coma. He was a man of 51 years who was first seen after a large haematemesis. Extensive oesophageal varicosities were found, but no other clinical or biochemical evidence of liver damage. At operation an old portal vein thrombosis, with recanalization, was found. The liver was macroscopically and histologically normal. A side-to-side portacaval anastomosis was constructed. One week after operation he became mentally abnormal, and lapsed into coma. The urine, which had previously been normal (Fig. 4a), now showed a heavy aminoaciduria (Fig. 4b). After five days in coma, he recovered consciousness after an intravenous infusion of 20 gm. of glutamic acid; the urine aminoacid pattern returned almost to normal (Fig. 4c). The episode of coma was repeated on two subsequent occasions, but each time recovery followed glutamic-acid therapy. He was finally treated with large doses of oral glutamic acid, and no further episode of coma occurred. The aminoacid changes in the urine were similar during each of the three periods of coma. Fig. 5. *Hepatic cirrhosis, coma, and recovery.* This figure shows the aminoacid patterns in two specimens of urine, during and after an episode of coma, from a female patient age 64 years, a chronic alcoholic. In the coma period (a) she was excreting very large quantities of cystine, penicillamine, β -aminoisobutyric acid, and ethanolamine. After she recovered from coma (b) the urine pattern of aminoacids returned to normal. At the time of the first urine analysis she was receiving

Figs. 1 to 6 represent the patterns of amino acids that may be found in normal urine and in the urine of patients with various types of liver injury. The sample of urine was placed at the bottom right-hand corner of the paper. Phenol was run from right to left as the first solvent, collidine-lutidine upwards as the second solvent. The circles indicate the final position of the aminoacids as revealed after treating the paper with ninhydrin. An arbitrary scale has been used in which the sizes and intensities of the aminoacid spots are represented by the sizes of the circles.

Key. 1, cysteic acid, from cystine; 2, penicillaminic acid, from penicillamine; 3, aspartic acid; 4, glutamic acid; 5, phosphoethanolamine; 6, glycine; 7, serine; 8, taurine; 9, alanine; 10, glutamine; 11, threonine; 12, histidine; 13, β -aminoisobutyric acid; 14, methylhistidine; 15, proline; 16, β -alanine, or citrulline; 17, unknown, 'under alanine'; 18, lysine; 19, arginine; 20, unknown, 'fast arginine'; 21, γ -aminobutyric acid; 22, α -aminobutyric acid; 23, valine; 24, leucine/iso-leucine; 25, phenylalanine; 26, tryptophane; 27, tyrosine; 28, ethanolamine; 29, methionine sulphone, from methionine; 30, methionine.

17, 'under alanine': as this compound resisted hydrolysis it cannot have been the peptide referred to by Dent (1947) under the same name.

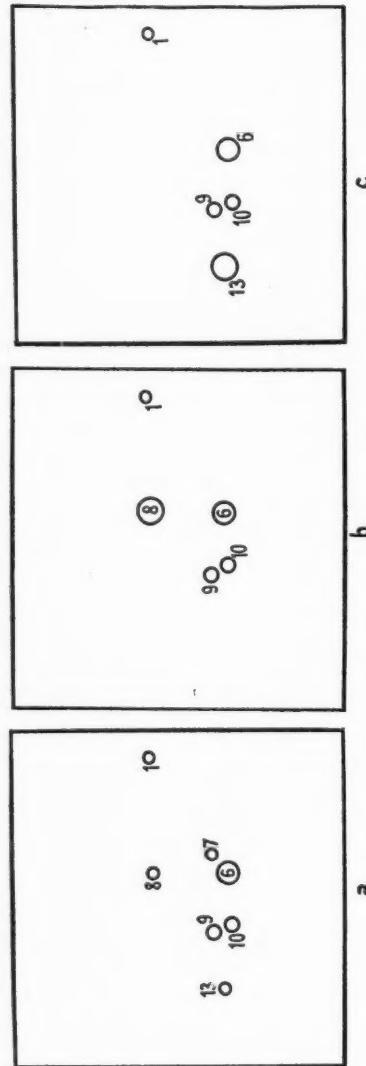
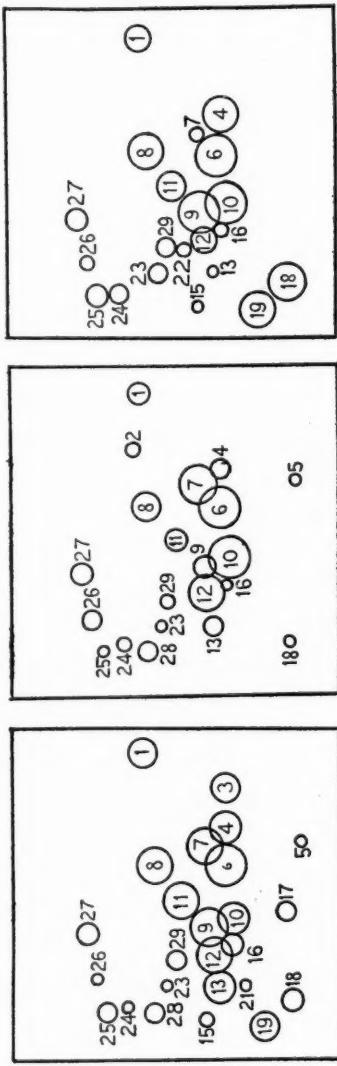
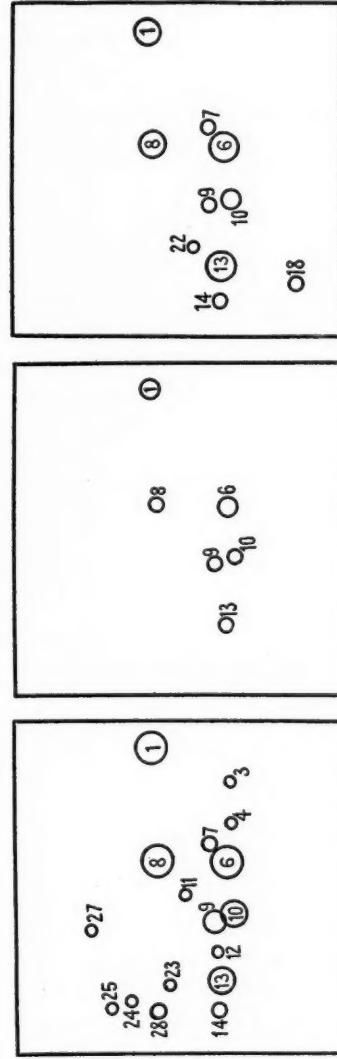


FIG. 1. The three different patterns of aminoacids found in 50 μ l. of normal urine, oxidized.



a

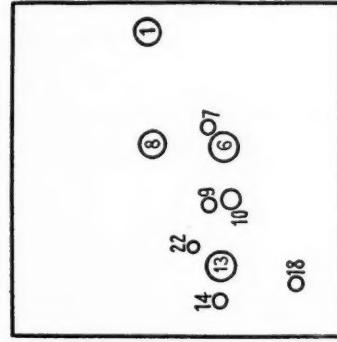
FIG. 2. Aminoacid patterns in the urine of three patients with massive hepatic necrosis; 50 μ l. urine, oxidized.



b

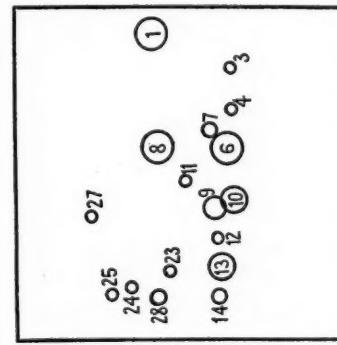
FIG. 2. Aminoacid patterns in the urine of a patient with cirrhosis (a) 27.4.50, (b) 16.6.50,
(c) 23.3.51. 50 μ l. urine, oxidized.

c

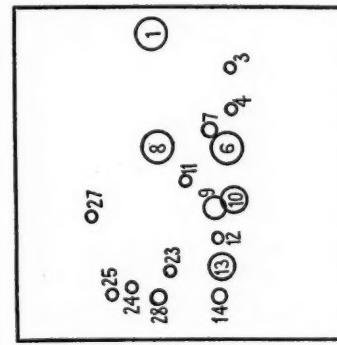


b

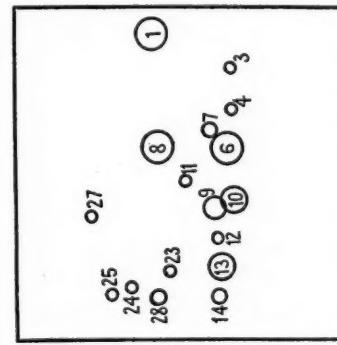
c



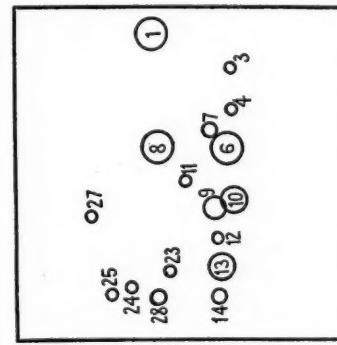
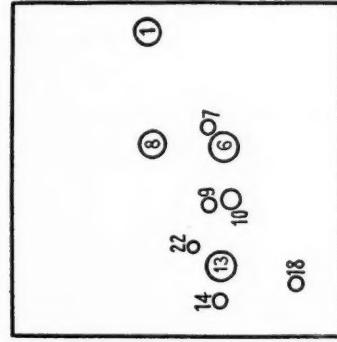
a



b



c



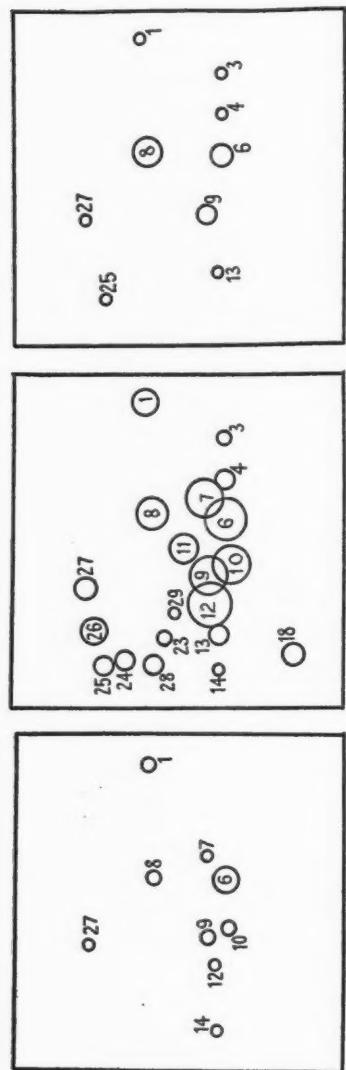


FIG. 4. The amino acids in the urine of a patient before (a), during (b), and after (c) an episode of hepatic coma.
50 µl. urine, oxidized.

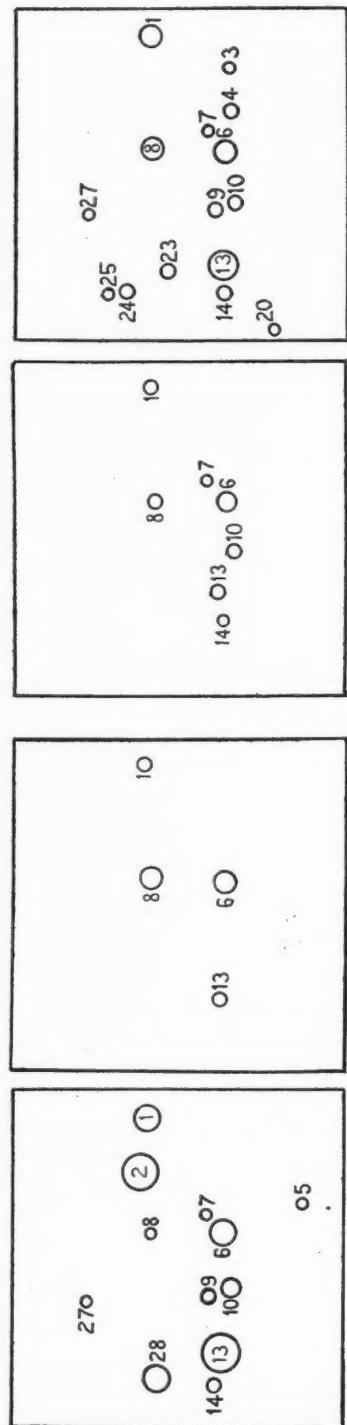


FIG. 5. Amino acid patterns in the urine of a patient with hepatic cirrhosis (a) in hepatic coma and (b) after recovery. 50 µl. urine, oxidized.

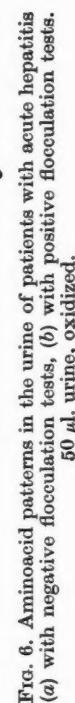


FIG. 6. Amino acid patterns in the urine of patients with acute hepatitis (a) with negative flocculation tests, (b) with positive flocculation tests. 50 µl. urine, oxidized.

AMINOACID METABOLISM FOLLOWING LIVER INJURY 503

300,000 units of penicillin twice daily by intramuscular injection. *Fig. 6a* shows the almost normal pattern of urine aminoacids from a case of serum hepatitis in a man aged 58 years. The liver histology is shown in Plate 36, Fig. 12. At the time of biopsy the serum-bilirubin was 11 mg. per 100 ml., and the cephalin-cholesterol and thymol turbidity tests were negative. *Fig. 6b* shows a moderate generalized aminoaciduria from a case of acute epidemic hepatitis. The patient was a woman aged 22 years. The liver histology is shown in Plate 35, Fig. 11. The serum-bilirubin was 3·2 mg. per 100 ml., and the serum flocculation tests were strongly positive.

Summary and Conclusions

The pattern of aminoacids in the blood and urine has been studied in normal persons and in 119 patients with acute or chronic liver injury.

More than 30 different aminoacids have been identified in the urine of patients with massive hepatic necrosis. The gross aminoaciduria that occurs in this condition usually, but not necessarily always, heralds a fatal outcome. Changes in the plasma pattern of aminoacids have also been demonstrated, but may appear less striking, because a relatively small rise in the concentration of one or more aminoacids in the plasma, above the renal threshold, may result in a considerable increase in their concentration in the urine.

In acute hepatitis the aminoacid excretion may show a small increase over normal in the more severe cases, but in many there is little or no detectable disturbance. An increased excretion of cystine is thought to be the most sensitive index of impaired aminoacid metabolism. Cases of hepatitis with a short, acute course, and strongly positive serum flocculation tests, appear more likely to show increased aminoaciduria than those which have a more insidious and prolonged course and negative, or only weakly positive, serum flocculation tests. It is suggested that this difference may be related to the anatomical situation of the lesion in the liver lobule.

In chronic hepatitis and cirrhosis of the liver a small number of patients showed disturbances in the pattern of aminoacids in the urine characterized by a well-marked increase in the concentration of two or three aminoacids. Such patients appeared to have active, progressive liver damage, and a correspondingly poor prognosis, although disappearance of the abnormal aminoacid pattern occasionally occurred and was associated with clinical remission.

Most of the aminoacids found in pathological urine specimens have been found in normal urine when a sufficiently large volume was taken for analysis.

No significant abnormalities have been found in the aminoacid metabolism of patients with obstructive jaundice or with focal lesions of the liver.

A new aminoacid, penicillamine ($\beta\beta'$ -dimethylcysteine), has been identified in urine. It is believed to be derived from penicillin administered therapeutically. It is excreted in greater amounts by patients with liver injury than by normal subjects receiving comparable doses of penicillin.

ADDENDUM

Since the present paper was written one further case of massive hepatic necrosis and three of chronic hepatitis in coma have been investigated. The case of acute necrosis occurred in a child of eight years who died after a three days' illness. One specimen of urine only was available for examination; this showed a very heavy aminoaciduria typical of the condition. Twenty different aminoacids were identified in 50 µl. of this specimen; all were present in greater concentration than the average for this group, shown by the figures in Table I. Of the three remaining cases, two were probably examples of hepatic cirrhosis following viral hepatitis. Samples of urine and plasma from one patient were examined before and during an episode of hepatic coma, and in the other case samples were obtained during coma and after recovery. Both patients showed a small but definite increase in the plasma-aminoacids while in coma, and a very striking increase of plasma-methionine, which became the aminoacid present in highest concentration. Glutamine was also seen to be present in excess of alanine, as noted earlier, and glucosamine was found in the plasma of the patient who died. In the patient who recovered, the concentration of methionine decreased, but remained in excess of normal. The last patient studied was a chronic alcoholic with cirrhosis and portal hypertension. When he was first seen his urine and plasma showed only a mild disturbance of aminoacid metabolism, the most notable abnormality being the high concentration of methionine. After a large haematemesis he lapsed into hepatic coma. At this time there was a gross aminoaciduria and aminoacidaemia. As in the other two cases, methionine increased out of proportion to the other aminoacids. After oxidation an unidentified sulphur-aminoacid was detected, moving to a position on the chromatogram midway between methionine sulphone and taurine. After three days in coma, and after receiving an intravenous infusion of glutamic acid, the patient recovered consciousness. During the following days his plasma-aminoacids returned to the pattern and concentration found before the haematemesis. Urine examined from a patient who had an equally severe haematemesis from a peptic ulcer did not show this disturbance of aminoacid metabolism, which cannot therefore be attributed simply to the presence of large quantities of blood in the intestine.

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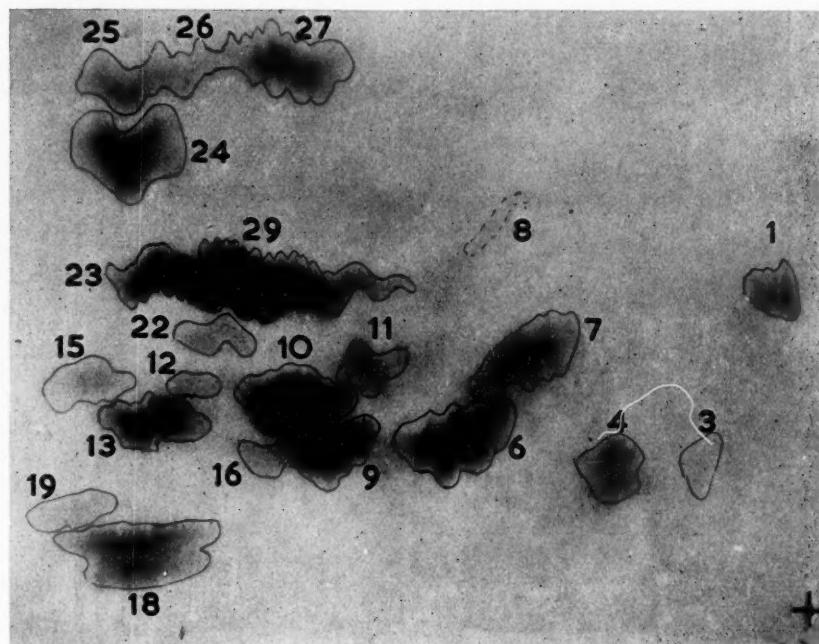


FIG. 7. Aminoacid chromatogram of the plasma of a patient with hepatic cirrhosis in coma; 625 µl. plasma ultrafiltrate, oxidized. There is a slight increase of all aminoacids, and a very great increase in the concentration of methionine, which has been oxidized to methionine sulphone (29)

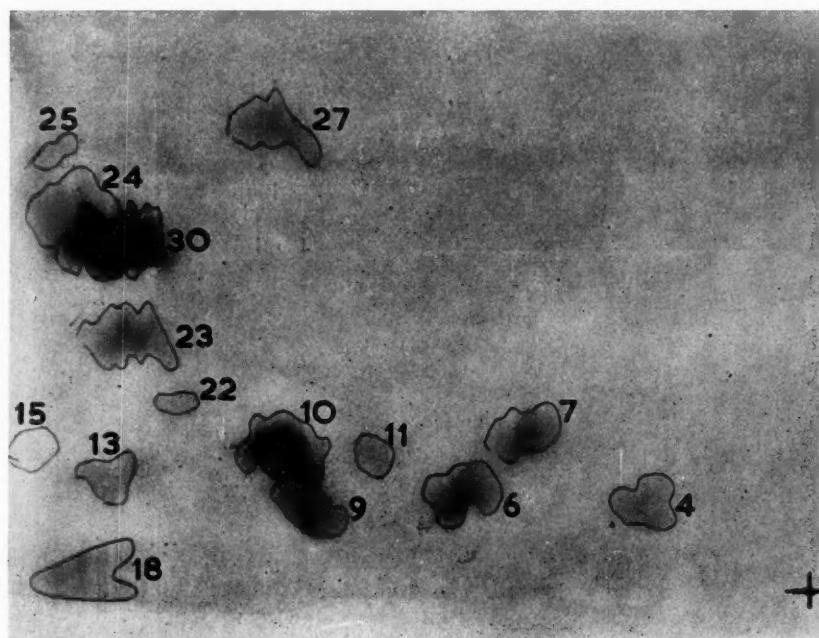


FIG. 8. Aminoacid chromatogram from the same patient; 125 µl. plasma ultrafiltrate, unoxidized. Note methionine in the unoxidized position (30)

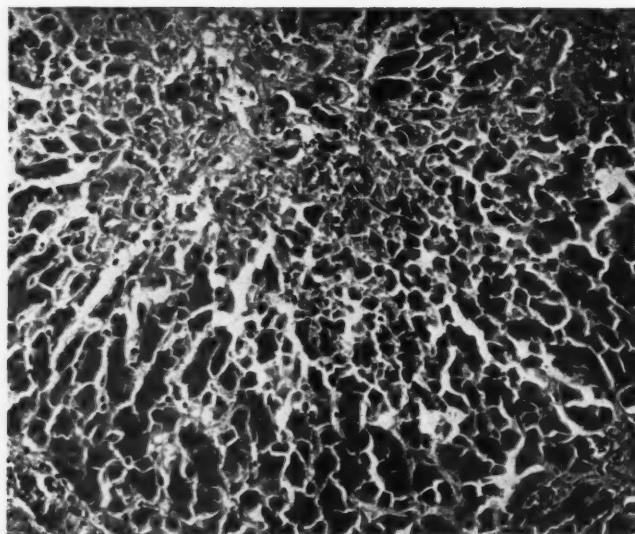


FIG. 11. Acute hepatitis with centrilobular necrosis. The serum flocculation tests were positive, and there was a moderate aminoaciduria (See Fig. 6b). Haematoxylin and eosin, $\times 150$

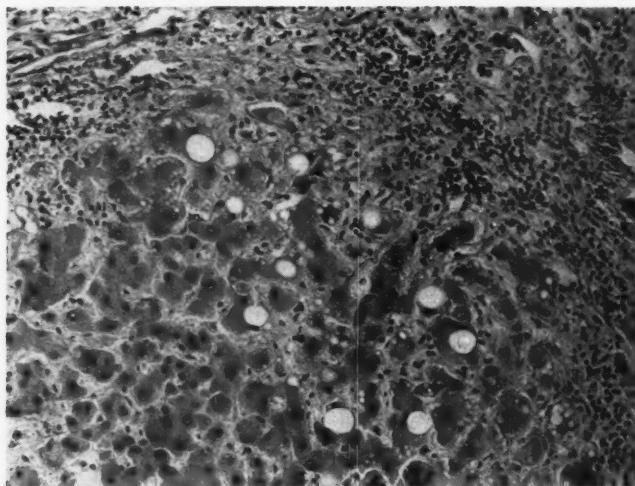


FIG. 10. Cirrhosis of the liver with coma. There was a marked disturbance in the pattern of the urinary aminoacids and a moderate increase in concentration (See Fig. 5). (Haematoxylin and eosin, $\times 150$)

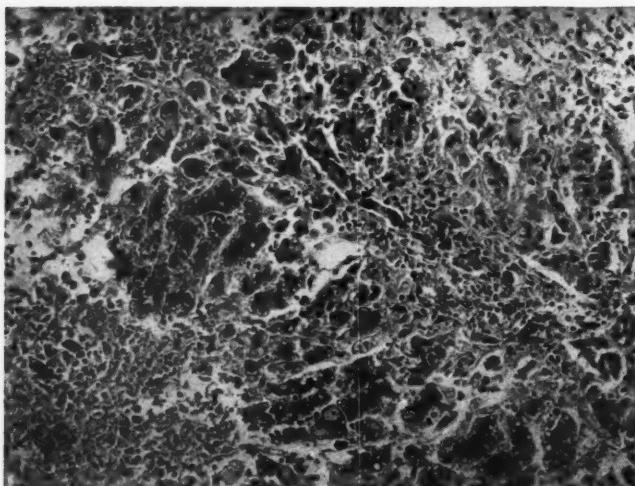


FIG. 9. Massive hepatic necrosis; an area of degenerating liver cells surrounded by necrotic and inflammatory cells. The urine pattern of this patient is shown in Fig. 2. (Haematoxylin and eosin, $\times 125$)

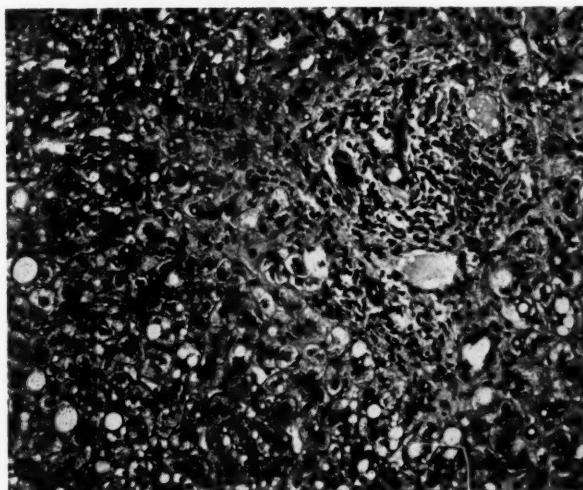
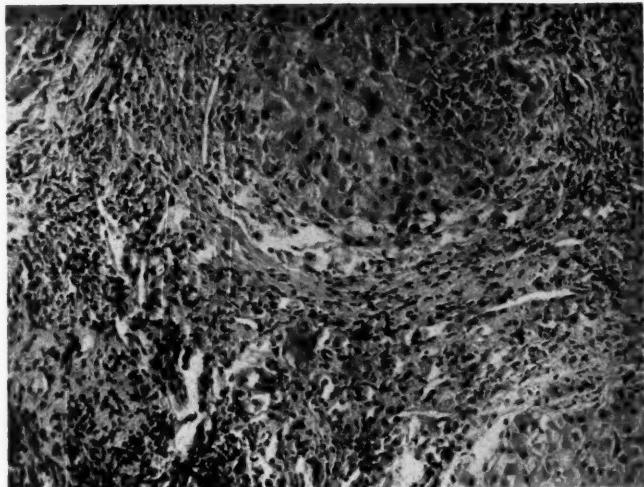
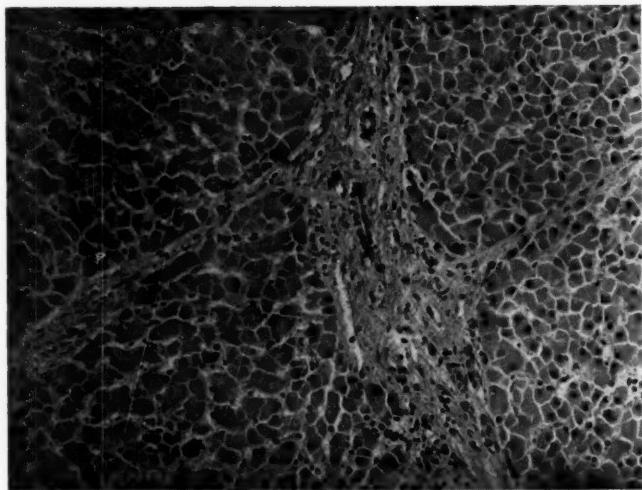


FIG. 12. Acute hepatitis. The section shows periportal inflammation and fatty infiltration. The serum flocculation tests were negative, and the urine amino-acids were almost normal (see Fig. 6a). (Haematoxylin and eosin, $\times 150$)

FIG. 13. 'Active' fibrosis. Young fibrous tissue and inflammatory cells can be seen surrounding a regeneration nodule. Fig. 3a shows the urine amino-acid pattern corresponding with this section. (Haematoxylin and eosin, $\times 150$)

FIG. 14. 'Inactive' fibrosis. Mature fibrous tissue disorganized the liver architecture; the parenchymal cells are normal. (Haematoxylin and eosin, $\times 150$)



THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN
AND IRELAND

1953

FORTY-SEVENTH ANNUAL GENERAL MEETING

THE FORTY-SEVENTH ANNUAL GENERAL MEETING was held in Newcastle upon Tyne on Friday and Saturday, May 22 and 23, 1953 in the New Chemistry Lecture Theatre, King's College. The attendance book was signed by 221 members. The proceedings began at 9.30 a.m.

The President, Dr. Gurney Yates, was in the Chair.

The Minutes of the last Annual General Meeting having been published in the Quarterly Journal of Medicine were taken as read, confirmed, and signed. The election of Officers, Executive Committee, Honorary Members, and Ordinary Members then followed.

Executive Committee

President. Professor F. J. Nattrass.

President-Elect. Professor Henry F. Moore.

Treasurer. Dr. C. Newman.

Secretary. Dr. C. M. Fletcher.

Members for England:

Dr. E. N. Chamberlain.

Professor R. V. Christie.

Dr. Terence East.

Professor C. Bruce Perry.

Dr. N. Lloyd Rusby.

Professor A. P. Thomson.

Members for Scotland:

Dr. J. D. S. Cameron.

Professor Stanley G. Graham.

Professor I. G. W. Hill.

Members for Ireland:

Dr. D. K. O'Donovan.

Dr. O. Fitzgerald.

Dr. R. W. M. Strain.

Election of Honorary Members

Dr. Hugh Barber.

Sir Francis Fraser.

Dr. T. L. Hardy.

Sir William Hume.

Professor A. E. Naish.

Dr. A. Gurney Yates.

Election of Ordinary Members

William Ferguson Anderson, M.D., M.R.C.P., Physician, Foresthill Hospital, Glasgow.
Thomas Harold Boon, M.D., M.R.C.P., Assistant Physician, Royal Victoria Infirmary, Newcastle.

John Arthur Cosh, M.D., M.R.C.P., Lecturer in Medicine, University of Bristol.

Charles Enrique Dent, M.D., M.R.C.P., Reader in Medicine, University of London, University College Hospital Medical School.

THE ASSOCIATION OF PHYSICIANS OF

Hewan Archdale Dewar, M.D., M.R.C.P., Assistant Physician, Royal Victoria Infirmary, Newcastle.

Alexander Peter Dick, M.D., M.R.C.P., Consultant Physician, Addenbrooke's Hospital, Cambridge.

Sheamus Dundon, M.D., F.R.C.P.I., Lecturer in Paediatrics, Royal College of Surgeons Medical School, Dublin.

Frank Abercombe Elliott, M.B., F.R.C.P., Assistant Physician and Neurologist, Charing Cross Hospital.

Alfred White Franklin, M.B., F.R.C.P., Physician, Children's Department, St. Bartholomew's Hospital.

John Carey Gilson, M.B., M.R.C.P., Director, Pneumoconiosis Research Unit, Llandough Hospital, Cardiff.

John Forrest Goodwin, M.D., M.R.C.P., Physician and Lecturer in Medicine, Post-graduate Medical School of London.

Francis Dudley Hart, M.D., F.R.C.P., Assistant Physician, Westminster Hospital.

Clifford Frank Hawkins, M.D., M.R.C.P., Assistant Physician, United Birmingham Hospitals.

John Louis Henderson, M.D., F.R.C.P.E., Professor of Child Health, University of St. Andrews.

Albert Thelwall Jones, M.D., M.R.C.P., Consultant Physician, Royal Liverpool United Hospitals.

Alan Robert Kelsall, M.D., M.R.C.P., Consultant Physician, West Herts Hospital Group.

Louis Philippe Eugene Laurent, M.D., F.R.C.P., Physician, West London Hospital.

Henry Johnston Scott Matthew, M.B., F.R.C.P.E., Assistant Physician, Royal Infirmary, Edinburgh.

John Harold Dundee Millar, M.D., M.R.C.P., Consultant Neurologist, Royal Victoria Hospital, Belfast.

Joseph Reginald Nassim, B.M., F.R.C.P., Physician, St. George's Hospital.

Charles Douglas Needham, M.D., M.R.C.P., Physician, Aberdeen General Hospitals.

John Erskine Grayhurst Pearson, D.M., F.R.C.P., Physician in Thoracic Diseases, Bristol Royal Hospitals.

Eirwyn Norman Rowlands, M.D., M.R.C.P., First Assistant, Department of Clinical Research, University College Hospital Medical School.

Robert Semple, M.D., F.R.C.P.E., First Assistant, Medical Professorial Unit, Middlesex Hospital.

Eric Walter Skipper, M.D., F.R.C.P., Physician, Sheffield Royal Infirmary.

Christopher Strang, M.D., M.R.C.P., Consultant Physician, Newcastle and Wansbeck Groups.

John Anderson Strong, M.B.E., M.B., M.R.C.P., Senior Lecturer in Medicine, University of Edinburgh.

Maxwell Telling, D.M., F.R.C.P., Assistant Physician, Leeds General Infirmary.

Sidney Charles Truelove, M.D., M.R.C.P., Assistant Physician, Nuffield Department of Clinical Medicine, Oxford.

John William Aldren Turner, D.M., F.R.C.P., Neurologist, St. Bartholomew's Hospital.

Allan George Williams Whitfield, M.D., M.R.C.P., Lecturer in Medicine, University of Birmingham.

The Treasurer, Dr. Charles Newman, in presenting the Annual Accounts for the year 1952, said he had sufficient money to support a larger Journal. DR. A. M. COOKE warmly welcomed this suggestion, which would help to expedite the publication of papers and reduce the backlog. The accounts were then adopted by the Association.

PROFESSOR W. MELVILLE ARNOTT raised the question of the relationship of the Association to Regional Societies of Physicians. There were now a number of such regional Societies and Associations, and it had occurred to members of the West Midlands Physicians Association that some informal recognition by the 'Parent Association' would be greatly appreciated. He suggested that it might become the custom for each regional Association to invite the President or other officers of the parent Association to their principal annual meeting. He suggested this custom might develop informally rather than being written into the constitution of any of the bodies concerned, but it would symbolize the unity of the whole body of consulting physicians in the country without forming any single large unwieldy group.

After some discussion, the President moved that this matter be referred to the Executive Committee, and this was agreed.

Place of Meeting, 1955 and 1956. The President pointed out that 1956 would be the 50th anniversary of the foundation of the Association. The provisional programme was to meet in London in 1955, and an invitation had been received from Manchester members to meet there in 1955 or 1956. He asked the sense of the meeting as to whether members would prefer to celebrate the 50th anniversary in London. After some discussion it was agreed to accept the Manchester invitation for 1955 and to meet in London in 1956.

The President then expressed the thanks of the Association for the excellent work done on its behalf by the retiring secretary, Dr. W. I. Card, and welcomed the new President, Professor F. J. Nattrass, who then took the Chair and called for a vote of thanks to the retiring President, Dr. Gurney Yates, which was passed with acclamation.

SIR RUSSELL BRAIN called the Association's attention to the fact that Dr. Parkes Weber had just celebrated his 90th birthday. It was agreed that a message of congratulation from the Association should be conveyed to Dr. Parkes Weber.

SCIENTIFIC BUSINESS

Friday Morning, May 22

1. PROFESSOR F. J. NATTRASS gave a short historical account of the Medical School of Newcastle, illustrated by lantern slides.

2. DR. J. D. ABBATT (introduced) and DR. RUSSELL FRASER reported the *Results of a Single-Dose Method of Radioiodine Treatment of Thyrotoxicosis incorporating a Drug Preparation*. The first 86 cases of thyrotoxicosis treated at Hammersmith Hospital had shown the practicability of this type of method; at the final assessment of these 86 patients, 78 per cent. showed a satisfactory remission, 23 per cent. needed retreatment, and 2 per cent. developed permanent myxoedema. The patients were first controlled with thiouracil, then given a radioiodine therapeutic dose and no further thiouracil. They were assessed provisionally at three months, and later at 12 months. A proportion were treated entirely as out-patients with full control of radiation hazard. After the standard drug preparation, the duration of stay of radioiodine in the thyroid gland was longer and less variable, clinical relief was quick, and subsequent clinical supervision easier than with patients prepared in other ways. Patients with large and nodular glands needed retreatment more frequently, and should probably receive a larger dose.

3. DR. E. M. McGIRR (introduced) and DR. J. M. HUTCHISON described *Radioactive Iodine Studies in Non-Endemic Goitrous Cretinism*. Radioactive iodine studies had been carried out on 13 patients with non-endemic goitrous cretinism, aged two to 20 years, who presented typical hypothyroidism with enlarged thyroids. All responded to dry thyroid given orally. Iodine-uptake studies showed that the thyroid glands accumulated radio-iodine excessively and rapidly. Potassium thiocyanate did not affect the iodine content, suggesting that inorganic iodine was being converted to an organic form. Release of radioiodine into the circulation was shown by reduction of gland radioactivity at 24 hours. Excretion of radioiodine was within the normal or hypothyroid range. Studies of protein-bound iodine gave high results at 48 hours, which are usually taken to indicate thyrotoxicosis. Only a proportion of this radioactivity was due to diiodotyrosine. The chemical nature of the remainder was not known, but on clinical grounds it could not be thyroid hormone, and in one case analysis of the radioactivity by column chromatography excluded the presence of thyroxine and triiodothyronine. These results confirmed American reports on similar cases in respect of radioiodine uptake, but the authors' patients were both able to convert inorganic iodine into organic iodine and able to release an organic iodine compound (not thyroid hormone) into the circulation. This suggested that non-endemic goitrous cretinism might occur from failure in final synthesis of thyroid hormone, a defect not previously described. The nature of this defect was obscure, but it might be familial. In view of these anomalous results the authors stressed that no laboratory test should take precedence over clinical assessment.

Communications 2 and 3 were discussed together.

DR. RUSSELL FRASER questioned whether Dr. McGirr's results did more than indicate a quantitative reduction in thyroid function, and suggested that chemical estimation of protein-bound iodine was necessary to show whether thyroid hormone was deficient in quantity or abnormal in composition. PROFESSOR E. J. WAYNE said that at Sheffield Mr. Blomfield, Dr. Macgregor, Dr Miller, and Dr. Weetch had treated 180 patients with

radioiodine. One hundred and forty-three patients had been followed up for more than six months, and 97 for more than one year. After full tracer studies in each case, a dose designed to be of 8,000 to 10,000 r.e.p. was delivered to the gland. The results were in general similar, and only 25 per cent. of patients had required more than one dose. In this series, in which few patients were given preliminary methyl thiouracil premedication, results as satisfactory as those of Dr. Fraser were achieved with a considerably lower order of radiation dose delivered to the gland.

In reply to Dr. Russell Fraser, DR. MCGIRR stated that it was unlikely that thyroid hormone was being produced. Despite the large amounts of protein-bound radioiodine the patients were hypothyroid, and yet responded well to dry thyroid given orally. The high urinary excretion values despite high gland uptake contrasted with low excretion in thyro-toxic subjects with high gland uptake, and suggested that the organic iodine compound released into the circulation was different in the two conditions, and was not being used but excreted in the cretins. Determination of the chemical basis of the radioactivity by column chromatography might provide a final answer.

4. DR. J. BADENOCH, DR. W. C. D. RICHARDS, DR. A. TURNBULL, DR. G. WAKISAKA (introduced), and DR. SHEILA CALLENDER discussed the use of *Radioactive Vitamin B₁₂ and Gastric Biopsy in the Diagnosis of Pernicious Anaemia and Subacute Combined Degeneration*. In pernicious anaemia the specimen of mucose taken from the body of the stomach by means of Wood's flexible gastric biopsy tube showed severe atrophy with intestinal metaplasia and interstitial cellular infiltration; normal body-glands were absent. The secretion of intrinsic factor could be assessed from radioactivity in the faeces after an oral dose of vitamin-B₁₂-labelled radioactive cobalt. With a test dose of 0.5 µg. of radioactive B₁₂, a mean of 87 per cent. of the radioactivity was recovered in 10 patients with pernicious anaemia, and a mean of 31 per cent. in 10 control patients with normal haematological findings. Sources of intrinsic factor given with radioactive B₁₂ to patients with pernicious anaemia considerably reduced the recovery of radioactivity, and it was therefore concluded that the difference between the recoveries in the patients with pernicious anaemia and the control subjects was due to the secretion of intrinsic factor by the latter. Five patients were described in whom these procedures had been of value in diagnosis. These patients presented the diagnostic problems of subacute combined degeneration of the cord without macrocytic anaemia, subacute combined degeneration apparently due to dietary deficiency of vitamin B₁₂, and pernicious anaemia during partial remission from previous treatment.

PROFESSOR L. J. WITTS thought that these techniques were of even more value for research than for diagnosis. It was now possible to discover whether vitamin B₁₂ was unabsorbed from the alimentary tract in a case of anaemia, and whether the defect could be corrected by intrinsic factor. Alternatively, patients with pernicious anaemia in remission could be used for assay of intrinsic factor.

DR. C. C. UNGLEY said he had found the discovery of normal gastric mucosa by biopsy valuable in excluding pernicious anaemia in doubtful cases, but atrophic mucosa did not establish the diagnosis. He and his colleagues had also used radioactive vitamin B₁₂, and agreed that consistently good absorption without intrinsic factor excluded pernicious anaemia, but again poor absorption did not prove that pernicious anaemia was present. They had obtained similar results after total gastrectomy in the absence of other evidence of the disorder. Deficient absorption might be found to be common in many patients with simple achylia. He congratulated the authors on their clear demonstration of the value of these methods both for research and for diagnosis.

DR. R. H. GIRDWOOD said that he, too, had been considering using radioactive vitamin B₁₂ in the investigation of the megaloblastic anaemias, but had been somewhat concerned by the concentration of radioactivity in the liver, and that even large doses of parenteral vitamin B₁₂ did not remove it. Since the half-life of ⁶⁰Co was about five years, he would be interested to have the views of Dr. Turnbull and his colleagues on the safety of these experiments.

DR. TURNBULL agreed with Dr. Ungley that when radioactive B₁₂ was given to a patient who had had a total gastrectomy, the recovery of radioactivity was similar to that found in patients with pernicious anaemia. However, he thought that it was generally believed that all such patients eventually develop macrocytic anaemia if they survive long enough. In reply to Dr. Girdwood, he said that the patient only received 0.2 microcurie, and that this was below levels considered dangerous by the Medical Research Council.

DR. BADENOCH, from an experience of more than 100 patients, said that a gastric biopsy which did not show the typical atrophy could exclude pernicious anaemia, but he had

seen atrophy of similar degree in one patient who had hypochromic anaemia with achlorhydria.

5. DR. C. M. OGILVIE (introduced) described some *Observations on the Use of Marsilid (1-Isopropyl, 2-Isonicotinyl Hydrazine) in the Treatment of Pulmonary Tuberculosis*. Sixty patients with pulmonary tuberculosis had been treated with marsilid at the London Hospital on a standard dose of 300 mg. daily. A control series of patients was being treated with isoniazid, but it was not yet possible to say which was the more effective. Plasma levels of marsilid approximately double those of isoniazid were obtained. Marsilid-resistant bacilli were recovered from seven of eight patients given marsilid alone for two months, and from only one of 14 patients treated for the same period with marsilid combined with 1 gm. streptomycin thrice weekly. Bacilli resistant to isoniazid were invariably resistant to marsilid. One patient with a resistant infection showed striking deterioration when treated with marsilid; the bacilli in this case were found to grow more profusely in high concentrations of isoniazid than in a drug-free culture medium. Marsilid induced much greater gains in weight than isoniazid, and appeared to have some effect upon appetite and weight independent of its effect upon the tubercle bacillus. Eight bacteriologically resistant patients gained weight on marsilid, three of them deteriorating in other respects, and one patient with extensive carcinomatosis had gained one and a half stone in eight weeks. The daily food intake was measured in several patients given marsilid, and rose to three to four times its original level within six weeks. The side-effects of marsilid were similar to those of isoniazid, but more frequent and troublesome; spontaneous clonic twitchings of the legs and hesitancy of micturition were the most frequent. No serious reactions were encountered and, except for one patient who developed a mild hepatitis, permanent withdrawal of the drug was never considered necessary. In half of the patients treated with marsilid, loss of weight, depression and irritability, insomnia, nightmares, and increased twitchings of the limbs appeared after the drug was discontinued, and persisted for several weeks.

PROFESSOR J. CROFTON said that isoniazid itself gave rise to large gains in weight, as compared with streptomycin and PAS. His group in Edinburgh had carried out controlled studies to determine whether isoniazid had a non-specific metabolic effect. Two groups of four volunteers received capsules containing either isoniazid or lactose (as control), without the individual knowing which he was receiving. The volunteers were weighed weekly, with their backs to the scales so as to avoid conscious or unconscious attention to diet. Over an eight-week period the controls gained a little more weight than those receiving isoniazid. This suggested that isoniazid increased weight by its effect on tuberculosis and had no specific effect on metabolism.

DR. SHEILA SHERLOCK asked whether there had been any evidence of glycosuria in the treated patients, especially in those who gained so much weight.

DR. OGILVIE replied that glucose-tolerance tests were done on six patients receiving marsilid; in five the curve lay at or below normal limits.

6. DR. R. L. RICHARDS discussed three aspects of the *Effects of Peripheral Arterial Embolism*. Pain was probably not always due to ischaemia of muscle, as Lewis believed. In some cases there was an initial, brief, local pain which coincided with the lodgement of the embolus. This was soon overshadowed by the constant ingravescent pain of ischaemia. Arterial spasm was often considered to be an invariable accompaniment of embolism. It was suggested that in most instances the so-called spasm was a normal response of the arteries distal to the embolus to the fall in intraluminal pressure which inevitably followed the occlusion of the main artery. During the first 72 hours after an embolic episode the muscles and joints of the ischaemic limb passed through a regular sequence of changes. Recognition of the stage which had been reached in this sequence was important if an accurate assessment of prognosis and of the need for urgent treatment was to be made. At first the muscles were of normal consistency; from six to 48 hours they became firm, contracted, and painful on passive movement; after 48 hours they became flaccid, and tenderness disappeared. Recovery was only possible up to the beginning of the second stage.

PROFESSOR P. C. P. CLOAKE asked Dr. Richards whether he accepted the evidence that papaverine applied to the wall of an embolized artery produced a vasodilatory effect. He drew attention to the results reported by Villaret and Cachera in experimental cerebral embolism in animals. These workers noted, after intravenous injection of powdered marble causing embolism of small cerebral arteries, that branches of the embolized vessels, and also of other vessels not derived from the embolized one, showed intermittent spasm over a prolonged period.

DR. GAVEY reported that in the patients he could recall who had had painless emboli, aortic incompetence or mitral incompetence was present, and the emboli had lodged in the upper limbs. Presumably the reason for the absence of pain was increased vascularity in the upper limbs due to the valve lesions; the situation was different in the lower limbs.

DR. R. E. SMITH said that only the biggest emboli could be diagnosed with certainty, that is those at the bifurcation of the aorta or in the femoral artery at its division into deep and superficial branches. In the latter position emboli often produced very small areas of gangrene, for example, in one or two toes. The state of the artery was important; if it was sclerotic the embolus would do serious damage.

In reply to Professor Cloake, DR. RICHARDS said that Kinmonth had shown that papaverine would only relieve spasm when applied directly to the arterial wall. With regard to cerebral embolism, he agreed that experimental work had shown that constriction could occur, which he thought might be in part due to the fall in blood-pressure and in part to neurogenic vasoconstriction, rather than spasm, which he defined as a violent constriction outside the normal range. He agreed with Dr. Smith that small emboli were often difficult to diagnose unless the condition was kept in mind.

2.15 p.m. Afternoon Session

In the afternoon a symposium on *Fibrositis, Neuritis, and the Intervertebral Disk* was held. PROFESSOR SIR HENRY COHEN, in opening the discussion, said that the clinical syndrome of pain, local tenderness (with palpable nodules), and stiffness, arising from known injury, infection, or gout, involving muscles, fasciae, joints, bursae, and tendon sheaths, had long been recognized; but there was a similar syndrome, commonly affecting the back (lumbago) or giving a stiff neck, unaccompanied by systemic disturbances, and often attributed to such vague aetiological factors as exposure to cold, draughts, chills, or undue physical strain. To this Gowers in 1904 gave the name 'fibrositis', and in 1920 Ralph Stockman described the histology of 'fibrositic' nodules and emphasized their inflammatory basis. These findings were seized upon, for in addition to providing a pathological basis for 'fibrositis', they could explain simply why, if the interstitial fibrous tissue of the larger nerves were similarly affected, pain was in the distribution of a nerve—'neuritis'. During the active inflammatory stage there would be tenderness on pressing on the nerve or stretching it, and evidence of disturbed function, such as paraesthesiae, weakness, or wasting; and when the inflammation resolved, adhesions might well result, giving a persistent pain ('neuralgia') for which stretching the nerve, or injecting saline solution to stretch the adhesions, was the proper treatment. Unfortunately this superstructure was built on very shaky foundations. Stockman's findings were never substantiated. The absence of an overt organic basis led later to psychological factors being indicated in the genesis of 'fibrositis', and many were the primitive and mystic symbolisms conjured up in support. Whatever be the prime cause of 'fibrositis' and 'neuritis', it had long been thought that (1) local mechanical factors, for example, in sciatica the sacroiliac ligament, spondylosis, abnormal intervertebral joint facets, narrowed intervertebral foramina, and (2) such reflex causes as pyriformis spasm, might play a part; but not before Mixter and Barr (1934) was the role of the intervertebral disk emphasized, first in the lumbar and later in the cervical sites. Here also less extravagant claims for surgery had more recently been made. The most important contribution to the problem was, however, our better understanding of the mechanism of pain, especially of deep pain, similar in quality, segmental in distribution, and accompanied by muscle-spasm whatever be the structure of origin, such as muscle, fascia, or viscous. The site of the lesion was determined by the factors which aggravated or relieved the pain, by accompanying symptoms or signs, and by the results of investigations. The labels 'fibrositis' and 'neuritis' should initiate, not conclude, a search for the cause of the patient's pain.

DR. D. H. COLLINS (introduced) discussed the *Pathological Anatomy of Fibrositis and Neuritis*. He said that the term fibrositis had no pathological justification. Biopsies of subcutaneous or deep painful nodules believed to be fibrositic usually revealed either histologically normal adipose tissue or, rarely, some other quite distinctive lesion such as dermatofibroma, polyarteritis nodosa, or metastatic carcinoma. He had personally examined more than one series of carefully located and removed nodules, with uninformative histological results. There was insufficient evidence in this material on which to base an opinion on the question of fat-herniation. The term neuritis was used by the pathologist to describe either myelin degeneration of peripheral nerves or interstitial reparative and chronic inflammatory changes. The term might be extended to include the focal interstitial changes seen in rheumatoid arthritis and some other diseases, but the relation of these

changes to painful manifestations was inexact. Dr. Collins went on to describe the nature of osteophytes arising in the spinal column. These were of two types, basically unrelated, and occurring together only by chance. The first type of osteophyte, and the most common, was that which arose from the margins of the vertebral bodies as a consequence of degeneration, protrusion, or collapse of the intervertebral disk. They formed beneath the periosteum raised from the lateral walls of the vertebral body by the slow or rapid bulging of relaxed annulus-fibres, or posteriorly by the escape of the nucleus pulposus. Vertebral-body osteophytes might affect one or many segments of the spinal column. When they were numerous the condition was known as spinal osteophytosis or spondylosis. The second type of osteophyte was that seen around the posterior intervertebral joints, and was a manifestation of osteoarthritis of these joints. These osteophytes were analogous to those at the margins of any other osteoarthritic joint, and pain might be due to true osteoarthritis of the apophysial joints. This state of affairs, however, was much less common than spinal osteophytosis of vertebral-body type. Spinal osteophytosis was not osteoarthritis, but resulted from some primary lesion of the intervertebral disk. Osteophytes of either or both types might impinge upon and diminish the intervertebral foramina. Post-mortem observation of the condition of the foramina and related nerves was of limited value, because many of the symptoms must depend upon the mobility of the various structures during life.

DR. J. H. KELLGREN described the *Pathological Physiology and Clinical Aspects of Fibrositis and Neuritis*. He said that fibrositis, or inflammation of fibrous tissue, was found constantly in rheumatoid arthritis, rheumatic fever, and other major rheumatic diseases, and might give rise to nodular lesions, particularly in the tendons and fasciae, but such lesions were an integral part of these diseases, and nothing was gained by distinguishing them as fibrotic. The term fibrositis was often erroneously used for the common post-traumatic or occupational pain in muscle or ligament. These painful states were not necessarily accompanied by any morbid anatomical changes at the source of pain, nor did we know anything certain about their pathological physiology. The faulty localization of pain arising from structures placed deeply in the back or limb-girdles, and the occurrence of 'referred' tenderness within the region where the pain was felt, made the exact definition of the source of pain most difficult, and provided a formidable obstacle to correct diagnosis and to experimental investigation. Idiopathic interstitial neuritis had been almost entirely replaced by our present concept of pressure or traumatic neuritis. In this there were two stages: a painful condition of the nerve-sheath analogous to the post-traumatic and occupational pain of muscle or ligament, and an interference with neuronal function which under certain conditions gave rise to an irritative nerve lesion. In a recent survey of rheumatic complaints in an urban population, it was found that over a five-year period the total complaint-rate was 330 per thousand. When classified by diagnosis, complaints attributable to osteoarthritis had a rate of 80, disk degeneration 45, disk prolapse 7, rheumatoid arthritis 30, and other diagnosable rheumatic conditions 58, leaving a rate of 110 for undiagnosable and mostly trivial painful conditions. It seemed preferable to refer to this last category as pains of undetermined nature, rather than to apply the label of fibrositis or neuritis, which implied a pathological process which is almost certainly absent from most of these cases.

SIR RUSSELL BRAIN discussed the *Clinical Aspects of Disk Lesion*. He said that a protrusion of a cervical intervertebral disk might occur either without, or with, X-ray evidence of cervical spondylosis. In the former group the protrusion might be either traumatic, as after a head injury, or spontaneous. Spontaneous cervical disk protrusion was often preceded by attacks of pain in the neck frequently labelled 'fibrositis'. A laterally placed protrusion, by compressing one spinal nerve, caused pain irradiating into the superficial and deep tissues innervated by the affected spinal segment. Sensory loss and motor symptoms were less conspicuous. The segmental tendon-reflexes were diminished or lost. The spinal cord was rarely involved, and the cerebrospinal fluid was usually normal. Pain in the neck was usually conspicuous, accompanied by muscle-spasm and limitation of movement. Plain X-rays often showed no abnormality, but a filling-defect might be present on myelography. Cervical spondylosis might cause an acute disk protrusion, with symptoms similar to those described above. Chronic radicular symptoms included pain, dysaesthesiae, and sensory loss, with muscular wasting and weakness and diminution or loss of tendon-reflexes, all with a distribution corresponding to the affected segments. The spinal cord was more often involved in cervical spondylosis. Trophic symptoms included the 'frozen shoulder'. The cerebrospinal fluid was usually normal. The X-rays of the neck showed the characteristic osteophytic protrusions, and myelography might show corresponding filling-defects. The effects of injury upon pre-existing cervical spondylosis might consist of either radicular symptoms alone or a mixture of radicular and spinal

cord symptoms. Acute protrusions of lumbar intervertebral disks were often preceded by 'lumbago'. Neurological symptoms might be either uniradicular or multiradicular. The roots usually affected were sacral 1, lumbar 4, or lumbar 5. The clinical picture might be predominantly sensory, as in typical 'sciatica' or 'femoral neuritis', or predominantly motor, leading to foot drop. The multiradicular picture was that of compression of the cauda equina below the level of the lesion, either unilaterally or bilaterally. The cerebrospinal fluid often showed a moderate increase of protein or, with large protrusions, even a complete block. Scoliosis and some spinal rigidity were commonly present, and radiography might show narrowing of the affected intervertebral disk or disks. Chronic protrusion of lumbar intervertebral disks was also a cause of 'lumbago'. The neurological picture was that of chronic compression of one or more spinal nerves on one or both sides. Pain and dysaesthesiae might be influenced by posture. A variable degree of cutaneous sensory loss, accompanied by muscular wasting and weakness and diminution or loss of the tendon-jerks in the lower limbs, was found. Narrowed intervertebral disk spaces and osteophytes were seen in the X-rays. Myelography was rarely necessary, but might show a filling-defect in either acute or chronic lumbar disk protrusion.

MR. G. F. ROWBOTHAM (introduced) discussed *Neurosurgical Aspects of the Problem*, restricting himself to consideration of the lumbar disk protrusion. His observations were based on a series of 710 laminectomies carried out in the Department of Neurological Surgery at the Newcastle General Hospital between the years 1941 and 1952. He had come to the conclusion that the diagnosis of herniated nucleus pulposus could safely be made only by exclusion; when all other lesions demonstrable by simple examination and investigation had been eliminated, eight out of the 10 remaining cases would prove to be a herniated nucleus pulposus. It was considered that selection for operation should be governed by the patient and his job, by the life history of the illness, and by the type of herniated nucleus pulposus. Details were given of the type of disk encountered at operation, of the nature of the operation performed for each type, and of the prognosis in each. Mr. Rowbotham was of the opinion that experience had shown that operative treatment was best restricted to the removal of a local sequestrum. In clinical terms, patients most suitable for operative treatment were those who were suffering severe back and sciatic pain, and who showed extreme scoliosis and restriction of spinal movement, without X-ray evidence of osteoarthritis or spondylolisthesis. Dealing with recurrences, Mr. Rowbotham said that he had no hesitation in operating again on patients who had the local sequestered type of disk, and in whom substantial relief had followed the first operation. He considered fusion of the spine to be of value, particularly where there was some spondylolisthesis. No one yet had been bold enough to lay down the criteria as to the stage in the history of a herniated nucleus pulposus at which an operation should be recommended. Although in the past there had been a tendency to operate in too many cases, the present mistake was to leave operation till too late, when the condition was incurable. Attention was finally called to the importance of adequate rest in the acute stage of the first attack of low back-ache and sciatica, if fewer intractable cases were to be produced. The communication was concluded by the showing of a coloured film illustrating the removal of a disk sequestrum.

MR. J. K. STANGER (introduced) discussed the viewpoint of the orthopaedic surgeon. He cast doubt upon the existence of fibrositis as a specific condition, regarding the term as one of convenience. He then referred to the various surgical causes of neuritis—not only root pressure due to prolapsed intervertebral disk, but also more peripheral conditions, such as pressure on the brachial plexus at the cervico-brachial junction, ulnar neuritis due to lesions at the elbow, and compression of the median nerve in the carpal tunnel. He quoted a recent review of 90 cases of prolapsed intervertebral disk, with the typical sciatica syndrome, in which operation had been done before 1951. In this survey the results had been rather more encouraging than had been supposed. The speaker felt that there was a case for operative exploration when adequate conservative treatment had failed. He then went on to describe non-operative measures used in the treatment of prolapsed intervertebral disk, including manipulation, plaster casts, and surgical braces. He finally mentioned the usefulness of spinal fusion in certain cases in which operative exploration had relieved sciatica but a low back disability persisted.

At 3.45 p.m. the meeting was adjourned for tea in the Victoria Royal Infirmary, where the following demonstrations had been arranged:

SIR RUSSELL BRAIN: 'Cervical disk protrusion'.

MR. G. F. ROWBOTHAM: 'Intervertebral disk lesions'.

DR. D. H. COLLINS: 'Disorders of intervertebral disks and spinal osteophytosis'.

DR. C. C. UNGLEY, DR. A. L. LATNER, DR. E. V. COX, DR. L. RAIN, and MR. McEVOY-BOWE: 'Studies in the separation of Castle's intrinsic factor from gastric juice by electrophoresis'.

DR. G. A. SMART, DR. A. L. LATNER, and MISS DOROTHY CHARLTON: 'Treatment of the nephrotic syndrome with ACTH'.

PROFESSOR J. B. DUGUID, MESSRS. A. E. YOUNG and E. V. HULSE, and MISS M. W. RICHARDSON: 'A method of assessing the respiratory surface of the lung'.

DR. G. DAVIDSON: 'Suprarenal hyperplasia'.

MR. D. N. WALDER and DR. T. E. BARLOW: 'Gastric blood-flow'.

PROFESSOR E. A. PASK and DR. L. MOLYNEUX: 'A simple pneumotachograph'. 'A simple positive-pressure respirator'.

DR. D. M. COURT, DR. F. J. W. MILLER, and DR. G. KNOX: 'Illness in infancy'.

At 5.0 p.m. the discussion of the symposium was resumed.

DR. RITCHIE RUSSELL pointed out that pain was the only reason for treatment in most of these cases. A nerve could be compressed without producing pain, and to attribute all the symptoms to nerve compression was an over-simplification of a difficult problem. Though the term 'fibrositis' should perhaps be discarded, he thought that the term 'neuritis' should be preserved, as it represented a clinical entity in which the nerve concerned was clearly in an abnormal state. He also emphasized the value of local injections of procaine as a means of breaking some of the 'pain cycles' which occur in this group of diseases.

DR. W. S. C. COPEMAN said that the term 'fibrositis' as generally used covered a number of clinical syndromes, at present little understood, in which pain was the common factor. In one of these syndromes, which he had described, the pain appeared to be dependent upon distension of fat tissue with non-inflammatory fluid in certain sites where free expansion is limited by a fibrous covering. The commonest sites were the normal fat-pads of the body and the iliac crests. This syndrome occurred most commonly in women, often around the menopause, and accounted for 2 to 5 per cent. of all cases of 'fibrositis' he had seen. When the fibrous covering became deficient for any reason, lobules of the oedematous fat might herniate and become partially strangulated, giving rise to tense tender 'nodules', with spasm of the surrounding muscles. This syndrome was often determined by cold or trauma, but was probably endocrine in origin.

DR. H. G. GARLAND said the Association had spent most of the afternoon discussing two medical myths, one of which was the mother of the other. As had already been pointed out, the word 'fibrositis' was invented by Sir William Gowers to explain the lumbar pain which usually accompanies sciatica. His general assumption was that sciatica was usually the result of 'sciatic neuritis', and that inflammation spread from the nerve to the fibrous tissues of the back. 'Fibrositis' was an analogy with 'cellulitis'. Gowers did not describe nodules, and these structures only became apparent during the next two decades. After 15 years, Stockman claimed to have removed some of these nodules and described their histology, but in retrospect it would appear that he had, in fact, only examined normal fibrous tissue and a thrombosed vein. From its inception, therefore, 'fibrositis' was a mythical invention, and nothing had happened in the succeeding years to establish it as either a clinical or a pathological entity, so that problems relating to its causation and treatment did not arise. 'Neuritis' seemed to be a somewhat similar myth, in that leprosy was the only undoubted inflammation of peripheral nerves. He was disappointed that Dr. Ritchie Russell found 'neuritis' a term acceptable for retention. As long as 'fibrositis' was retained, the true nature of the patient's symptoms must go undetected and, in fact, this unhappy term was frequently applied to any kind of painful condition, often with serious results to the patient. A diagnosis of 'neuritis' was usually made in a patient suffering from an isolated peripheral nerve-palsy, but since such conditions were never inflammatory the true cause of the paralysis remained undiscovered. Both these terms were therefore meaningless and dangerous.

DR. G. D. KERSLEY, while he agreed that the diagnosis of fibrositis could be the 'refuge of the diagnostically destitute' or the 'loose thoughts of the lazy', believed that a syndrome existed in people who were psychologically stable, who developed intermittent attacks of acute myalgia and muscle-spasm in various places, often with changes in the weather or local chill, and sometimes with infection. To ignore this syndrome because it was unexplained was to bury one's head in the sand. The investigation of this condition presented, however, the greatest difficulty. In his hands hydration, using pitressin, made patients feel ill; ACTH temporarily improved some, but the euphoric effect could not be neglected.

in the assessment; intravenous hypertonic saline appeared to produce some benefit, but control was so difficult that results not based on a very large series were almost worthless.

DR. L. P. E. LAURENT commented upon the condition of *meralgia paraesthetica*, which was usually attributed to compression of the nerve as it passed through the *fascia lata*, but he did not believe this was true because it was not always relieved by decompression.

PROFESSOR S. ALSTEAD said he did not underrate the danger of using the word 'fibrosis' as a general rag-bag for ill-defined maladies beyond the diagnostic powers of the doctor. Nevertheless the absence of histological changes sufficiently gross to convince a morbid anatomist should not be regarded as disproving the existence of the disease. There were a number of clinical phenomena which could not be disposed of so easily. He referred to the fairly well-defined sites of election for 'fibrosis'. The pain often followed an exacerbation of infection such as those of the respiratory tract (lumped together as 'influenza'), cholecystitis, and other febrile illnesses, and could be relieved by appropriate treatment, including physiotherapy.

DR. F. G. LESCHER and DR. R. W. D. TURNER also spoke.

In conclusion SIR HENRY COHEN thanked all the contributors to the discussion, which he was sure everyone had found stimulating.

Annual Dinner

The Annual Dinner was held in the Old Assembly Rooms. The President, PROFESSOR F. J. NATTRASS, was in the chair. The toast of the Association was proposed by the President, and that of the guests by SIR JAMES SPENCE. SIR ROBSON ROWELL replied, and the toast of the President was proposed by PROFESSOR T. L. HARDY. The President responded.

Saturday, 9.30 a.m. Morning Session

7. DR. P. D. BEDFORD (introduced) recorded some *Adverse Cerebral Effects of Anaesthesia on Old People*. He cited typical examples of 23 old people in whom serious cerebral damage had occurred during operation under general anaesthesia. All the patients had been normal before the operation, and were virtually decerebrate following it. He discussed some of the factors he held responsible for this damage, and quoted case-reports of patients who had not been operated on, to illustrate the irreversible cerebral damage due to states of lowered blood-pressure following haemorrhage and coronary thrombosis. He quoted an example of irreversible damage to the brain which had occurred in a young person, to illustrate the danger of anoxia and to show that serious ill effects during anaesthesia occur in the young as well as the old. He considered that 'hypotensive surgery' was contra-indicated in the elderly until proof was forthcoming that it was innocuous not only with regard to survival, but also with regard to the subsequent mental state of the patient. He indicated the part played by potent analgesic and hypnotic drugs in routine use in causing confusion in elderly people, and pointed out the danger of giving these drugs to allay the very confusion which they caused. Finally, he discussed the management of post-operative confusion in elderly people.

DR. L. P. E. LAURENT thought Dr. Bedford's communication was important and timely in view of the frequent use of hypotensive drugs. He drew attention to a book on the subject of cerebral anoxic damage (C. B. Courville, *Untoward Effects of Nitrous Oxide Anaesthesia*, 1939, Mountain View, California) where the pathology was fully described. Dr. Laurent pointed out that similar permanent cerebral damage might follow the repeated use of morphia in an old person, and quoted a personal case where gr. $\frac{1}{4}$, given three times in 12 hours to a woman of 65 after a fracture, resulted in virtual decerebration.

8. DR. JOHN RICHARDSON and DR. JOHN PINNIGER (introduced) discussed *Some Further Evidence on the Interrelationship between the Leukaemias, Polycythaemia Vera, and Myelofibrosis, with special reference to the Value of Rib Biopsy*. They described the removal of a section of rib as a simple and safe method of marrow biopsy, and showed that this provided information on bone framework as well as on the haemopoietic cells contained in it, which needle biopsy or trephine methods did not. By treating material thus obtained with a silver-impregnation stain, unsuspected fibrosis had been demonstrated. Illustrative cases were quoted, the first being one of polycythaemia, myeloid leukaemia, and myelofibrosis. The second patient suffered from atypical myeloid leukaemia and myelofibrosis, the third had typical myeloid leukaemia and myelofibrosis, and the fourth died of acute myeloid leukaemia with myelofibrosis. The fifth suffered from aleukaemic lymphatic leukaemia and myelofibrosis. The first two patients died of miliary tuberculosis.

Cases 1 and 3 had radiotherapy to the spleen, Case 2 had a splenectomy, Case 4 had an impalpable spleen, and the spleen in Case 5 was only occasionally felt. Thus in three cases treatment was directed to the spleen, and in the other two the spleen was not significantly enlarged. The view was put forward that the leukaemias, polycythaemia vera, and myelofibrosis were all variants of proliferative disorders stemming from the primitive mesenchymal cell, the pattern depending on the predominant cell-types and stage of development involved. They could occur as independent pathological entities, but frequently presented as mixed hyperplastic states. It was suggested that the presence of splenomegaly depended on the proliferative process affecting the spleen, and not on extramedullary erythropoiesis, and that the decision to remove the spleen, should it be causing haemolysis, was not as dangerous as was often thought.

DR. BODLEY SCOTT was able to confirm the value of rib biopsy. He had long believed that myelosclerosis had to be included in the group of proliferative diseases of the mesenchyme, and that fibrosis was an integral part of the morbid process, as it was in Hodgkin's disease. One variant, chronic erythromyelosis, often showed the blood changes of chronic myeloid leukaemia and polycythaemia, with radiological evidence of osteosclerosis.

9. DR. H. GOADBY reported his experience of the *Control of Tromexan Therapy in Coronary Thrombosis*. He had used tromexan anticoagulant therapy in 57 cases of coronary thrombosis, ischaemic heart disease, and other cardiovascular conditions, without controlling the dose by repeated prothrombin-time estimations. If tromexan could thus be used safely and effectively, domiciliary therapy would be possible without readily available laboratory facilities. The course of tromexan was heavy: first day 1,200 mg., second day 900 mg., third day 600 mg., and then 900 mg. daily until the end of treatment. The urine was examined microscopically for red cells every day; more than one per high power field was taken to indicate overdosage; the tromexan would then be stopped for 24 hours. If 900 mg. daily again produced haematuria, the dose was lowered. The method was probably safe. Red cells appeared in the urine of 21 patients, at prothrombin times ranging from 30 to 100 seconds. One patient, who had tromexan for thrombophlebitis following oesophagogastrectomy, died with a haemopericardium due to the suture line giving way. This was possibly attributable to tromexan. Another patient had a haematemesis from a subsequently proven peptic ulcer: there had been red cells in the urine on the third day of tromexan therapy. It was felt that these incidents did not indicate that the method was very likely to produce uncontrollable or fatal haemorrhages. The assessment of effectiveness of the treatment had been made in three ways. First, prothrombin times: these had been estimated once every five to seven days, without the results being disclosed at the time. Although this is the conventional measurement, it is known that the prothrombin time in any one patient, on constant tromexan dosage, may vary widely from day to day, or even through the day. Casual samples therefore are unreliable. Second: appearance of red cells in the urine, or other signs of a haemorrhagic state. He required further observation to decide whether or not this method is adequate. Third: the prevention of further thrombosis in the coronary arteries or leg veins. As was the experience of many other workers, further thrombosis had occurred during treatment, even on a day when prothrombin time was much prolonged or there were red cells in the urine.

DR. A. G. OGILVIE did not agree that microscopic haematuria was necessarily the first sign of impending haemorrhage, which would be a serious risk in Dr. Goadby's method.

DR. ALEXANDER BROWN agreed that the need for a simple method of controlling anticoagulant therapy was widely admitted. Nevertheless, there were certain aspects of this treatment which required more attention than could usually be given in general practice. All the anticoagulant drugs were potent and capable of harm if misused, and there was little safety margin between the optimal therapeutic effect and the danger of serious haemorrhage. Even with careful laboratory supervision, the reported incidence of bleeding with 'prothrombopenic' drugs was 1 to 3 per cent. Furthermore, certain conditions, which might not be clinically obvious, were capable of accentuating the response to anticoagulant drugs. Probably the most important of these was renal insufficiency, even of moderate severity. In such circumstances not only was the anticoagulant effect enhanced, but there was also an increased tendency to haemorrhage which might be due to the toxic influence of renal disease on the blood-vessels. This applied as much to heparin as to the coumarin derivatives and phenylindandione. Severe haemorrhage after a single therapeutic dose of dicoumarol in a patient with renal disease had been reported. He had had a patient with asymptomatic renal insufficiency who received a single dose of 10,000 units of heparin intravenously. The coagulation time rose above one hour, and remained above the accepted therapeutic level for nearly two days. He had been so impressed with the influence of mild renal insufficiency on the response to anticoagulant therapy that he had made it a

routine practice to scrutinize the urinary output and to have the blood-urea estimated in patients to whom anticoagulant was to be given. No thrombo-embolic disease was 100 per cent. fatal, and anticoagulant therapy did not always prevent untoward sequelae. Any relaxation of control, which might detract from the efficiency of the treatment and increase the risk of a therapeutic misadventure, was unwise.

DR. A. M. COOKE felt that Dr. Goadby should be congratulated on his attempt to make anticoagulants practicable in the patient's home, and thought that, although there were undoubtedly dangers from the unpredictable response of very ill patients to anticoagulants, and occasional accidents from haemorrhage, such as from unsuspected gastric ulcer, the domiciliary method was most likely to be useful when the patient had previously been in hospital and had been discharged with a stable prothrombin level.

In reply DR. GOADBY agreed that a careful watch should be kept for any signs of haemorrhage. He did not wait for red cells to appear in the urine if there was a haematemesis! The work would continue, and he hoped to adopt Dr. Cooke's suggestion.

10. DR. D. HUBBLE discussed *Chronic Insulin Insufficiency in Diabetic Children*. He said that retarded growth in diabetic children might be due to: (1) Deficient protein anabolism resulting in hypopituitarism. (2) Increased protein catabolism, due to lack of endocrine balance resulting from insulin insufficiency (Mauriac's syndrome). (3) Disordered protein metabolism, as in the complications of diabetes, for example, nephropathy. One example of diabetic hypopituitarism and three examples of the Mauriac syndrome were discussed. The characteristic features of the Mauriac syndrome were retarded growth, obesity, florid facies, hepatomegaly, and hypercholesterolaemia. The enormous liver of a patient who had died had been shown to contain a large excess of glycogen and a slight excess of fat. The syndrome could be both prevented and cured by the use of long-acting insulin. Normal growth was resumed, and by eight-day nitrogen balances in two patients it had been shown that nitrogen debits could be reversed when protamine-zinc insulin was used. The metabolic paradoxes of the Mauriac syndrome could be explained by lack of endocrine balance, insulin insufficiency, and consequent corticosteroid excess.

DR. W. G. OAKLEY said that he did not think that undernutrition alone could account for dwarfism in diabetes, and, although careful control often improved the condition with decrease in the size of the liver and increase in height, it did not cure it. The presence of glycogen in excess in the liver was of interest, as a similar condition had recently been found by liver biopsy in two poorly controlled adult diabetic patients with hepatomegaly. With regard to treatment, emphasis had been laid on the importance of protamine-zinc insulin in the maintenance of good control in children, but in a survey of over 200 long-standing cases the best results had been found in patients treated throughout with two injections of soluble insulin.

DR. A. M. COOKE thought that many so-called diabetic dwarfs were not suffering from an endocrine dyscrasia, but from simple lack of food. He had also found that Mauriac's syndrome responded well to protamine-zinc insulin and high protein feeding.

DR. GEORGE GRAHAM said that he did not think that the poor control of these diabetic conditions was really responsible for the failure to grow, though it would affect the general condition unfavourably. He thought the failure to grow was due to some other cause. He had known children who had had poor diets and also poor control, who had grown well, while others with good diets and good control had grown poorly.

In reply, DR. HUBBLE said that there was no dietetic deficiency in these patients, who were on 'free' diets; nor was such deficiency recorded in the literature. Protein deficiency might contribute to hypopituitarism, but deficient diets could not account for obesity or for an excess of glycogen in the liver.

11. PROFESSOR A. BRADFORD HILL (introduced) and DR. J. H. KELLGREN reported a *Comparison of Cortisone and Aspirin Therapy in Early Cases of Rheumatoid Arthritis*. A small but strictly controlled therapeutic trial of cortisone and aspirin as suppressive agents in early cases of rheumatoid arthritis had been begun under the Medical Research Council. Taking such early cases, uncomplicated by severe anatomical changes in the joints or by metabolic or endocrine disturbances resulting from prolonged illness, the object of the trial was (1) to compare cortisone with aspirin as agents for relieving symptoms and improving functional capacity, and (2) to study the evolution of the rheumatoid process during prolonged therapy, and the effects of withdrawal of treatment. Only patients with disease of three to nine months' duration had been accepted. They were required to have polyarthritis of rheumatoid type affecting at least four joints, and bilateral involvement of either hands, feet, ankles, or wrists. Such patients, admitted to six centres in Great Britain,

were initially divided by sex, age, and disease duration. Within each of these sub-groups the choice of treatment with cortisone or aspirin was determined at random. Treatment was given in 12-week courses, separated by one week off treatment. A short period of standard dosage was followed by individual dosage aimed at restoring maximum functional efficiency without producing serious side-effects. The results were being assessed clinically by general functional capacity and by joint tenderness and range of movement. Measurements of strength of grip, two tests of dexterity, laboratory observations, and estimations of erythrocyte sedimentation rate and haemoglobin level, were also being made. There were 14 juvenile patients (16 years or younger), of whom eight were receiving cortisone and six aspirin. In the adult group (17 to 59 years) there were 30 patients having cortisone and 31 having aspirin. For the adult group it had been possible to analyse the records relating to the first 12 weeks of treatment and the ensuing week of observation. Both treatment groups revealed significant improvement in most of the measured features, followed by a relapse in the week off treatment. The cortisone group revealed a rather greater improvement in the haemoglobin level and blood sedimentation rate, but in other respects the two treatment groups did not, at this first stage, differ materially.

DR. G. D. KERSLEY uttered a warning against the swing of the pendulum, and urged that the finding that aspirin was at least as useful as cortisone in one type of rheumatoid arthritis, when administered in one way, should not be considered to indicate that cortisone was of no value in any rheumatoid condition. He felt that experience, and the theory of its purely antiphlogistic rather than anti-rheumatic effect, suggested that long-term intermittent treatment of the early slowly progressive case was perhaps the least likely to be of benefit. The 'covering' of an acute episode or period of stress, a temporary use during a period of rehabilitation or correction of deformity, and treatment when a flare-up occurred after operation, were the clinical indications for the use of cortisone in rheumatoid disease.

DR. W. A. BOURNE wondered whether the notable tendency to spontaneous remission in these cases might not be masking the effect of therapy.

12. DR. P. FOURMAN (introduced) described the *Production of Oedema in Deficiency of Potassium*. Deficiency of potassium had been experimentally induced by giving a cation-exchange resin to five volunteers. After the period of deprivation sodium had been given in normal amounts, but a low-potassium diet had been maintained. Dr. Fourman found that sodium rapidly replaced the potassium lost from cells. Sodium then accumulated with chloride in the extracellular fluid. Oedema appeared in three of his subjects. When potassium was given it was retained, and sodium began to leave the cells, but it did not leave the body. The accumulation of extracellular fluid was not discharged until the deficiency of potassium had been completely made good. The symptoms of potassium deficiency largely remitted when sodium had replaced potassium in the cells, and the electrocardiograms, which had been typical of potassium deficiency, became more normal, but tetany appeared in two of the subjects. Unexplained oedema or tetany might occasionally be the result of an unsuspected deficiency of potassium.

This communication was discussed by PROFESSOR R. PLATT.

13. DR. J. L. GIBBONS (introduced) and DR. H. G. MILLER discussed the *Treatment of Acute Diseases of the Nervous System with ACTH: Acute Disseminated Encephalomyelitis and Acute Exacerbations of Disseminated Sclerosis*. Although acute disseminated encephalomyelitis and acute disseminated sclerosis might present similar clinical pictures, recent follow-up studies in Newcastle had confirmed that there was a marked difference in prognosis between the two conditions. That they were indeed distinct diseases was also suggested by the results of experimental treatment of both illnesses with ACTH. Physiologically effective dosage of this drug over the course of five days was followed by unequivocal clinical improvement in 10 of 13 patients with encephalomyelitis recently treated; in eight instances such improvement was evident within 12 hours of the first injection. Similar courses of the drug had been given in eight acute exacerbations of established disseminated sclerosis without benefit to the acute symptoms.

14. DR. H. A. DEWAR, DR. S. G. OWEN, and DR. A. R. JENKINS (introduced) described the *Effects of Hexamethonium Bromide on the Cerebral Circulation in Hypertension*. Cerebral blood-flow had been estimated by the nitrous-oxide method in six patients suffering from arterial hypertension, before and after administration of hexamethonium bromide. The mean arterial blood-pressure fell by an average of 30 per cent., but no significant change occurred in mean cerebral blood-flow. Reasons were given why it seemed unlikely that the fall which occurred in cerebral vascular resistance was due to paralysis of the cervical

sympathetic ganglia. The rate of cerebral oxygen utilization was measured in four of the patients, and showed no essential alteration. The implications of these findings were discussed in relation to the risk which hypertensive patients might run of developing cerebral thrombosis while they were being treated with methonium compounds.

DR. SHEILA SHERLOCK said that it was difficult to know how hexamethonium exerted its effect on the blood-pressure. It did not alter cardiac output, at least in the recumbent posture. Dr. Dewar and his colleagues had observed little change in cerebral blood-flow; Dr. de Wardener and his group found a virtually unaltered renal blood-flow after hexamethonium. The splanchnic area seemed the most likely site of vasodilatation, but her observations had shown that there was no splanchnic vasodilatation after hexamethonium, but that splanchnic blood-flow fell *pari passu* with the fall in systemic blood-pressure. There was certainly cutaneous vasodilatation, but it was difficult to account for the fall in blood-pressure by this alone.

15. DR. J. G. MACARTHUR (introduced) and PROFESSOR S. ALSTEAD described an experimental study of the *Relative Merits of Rubefacients and Counter-irritants*. The injection of strong saline into the deep tissues was a particularly useful method for experimental purposes, because it produced 'a continuous pain which resembles more closely the pain of disease than does the momentary pain produced by exploration with needles' (Kellgren). This provided the starting-point for observations which they had made on themselves as experimental subjects. A series of control tests established the character and duration of the pain, its predictability, and the minimal effective concentration of saline. Attempts were then made by various procedures to influence this saline-induced pain: these included the application to the skin of suitable preparations of (1) volatile oil of mustard, and (2) esters of nicotine acid. Radiant heat and continuous galvanism applied to the skin provided simple and convenient methods for demonstrating the phenomenon of counter-irritation. Next it was shown that the powerful irritation of volatile oil of mustard on the appropriate area of the skin could abolish or greatly mitigate the deep pain caused by intramuscular injection of strong saline. The esters of nicotine acid, though causing intense cutaneous vasodilatation, were almost useless for the relief of pain.

This communication was discussed by DR. J. H. KELLGREEN, DR. A. H. IMRIE, and DR. J. G. SCADDING.

On Saturday afternoon a party of members visited the Roman Wall under the guidance of Professor I. A. Richmond.

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